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AMGEN INC.
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

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HOWARD, ZACHARY C	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/444,790
Filing Date: May 19, 1995
Appellant(s): BROCKHAUS ET AL.

Sharon M. Sintich
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 28 February 2008 (02/28/2008) appealing from the Office action mailed 23 February 2007 (02/23/2007). This replaces the Examiner's Answer mailed on 14 August 2008 (8/14/2008) in view of the 9/23/08 decision for the Petition filed on 28 August 2008 (8/28/2008) and on reconsideration, it is decided that the first petition was fully persuasive and therefore this new Answer is

being sent which omits reference to the potential new rejection which was originally denied.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief of 28 February 2008, at page 4.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement at page 4 of the status of claims contained in the brief (of 28 February 2008) is correct.

(4) Status of Amendments After Final

The appellant's statement at page 4 of the status of amendments after final rejection contained in the brief (of 28 February 2008) is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief (of 28 February 2008 at pages 4-9) is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement (at page 10 of the brief of 28 February 2008) of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief (of 28 February 2008) is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, official notice, and admitted prior art) relied upon by the examiner in the rejection of claims under appeal.

Smith, C.A. et al. "A Receptor for Tumor Necrosis Factor Defines an Unusual Family of Cellular and Viral Proteins" Science, vol 248 (May 25, 1990), pp. 1019-1023

Dembic, et al. "Two Human TNF Receptors Have Similar Extracellular, but Distinct Intracellular, Domain Sequences" Cytokine, vol 2, no. 4 (July 1990), pp. 231-7

Chan, F. K. et al. "A Domain in TNF Receptors That Mediates Ligand-Independent Receptor Assembly and Signaling" Science, vol 288 (June 30, 2000), pp. 2351-2354.

5395760	SMITH et al.	3-1995
5116964	CAPON et al.	5-1992

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112, 1st paragraph, written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121 and 123-137 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to (1) determine what the claims as a whole cover; (2) review the application to understand how it provides support for the claimed invention including each element; and (3) determine whether one skilled in the art would recognize that the Appellant was in possession of the claimed invention as a whole. See page 1 of the Written Description Training Materials Revision 1, 3/25/2008 (http://www.uspto.gov/web/menu/written.pdf).

(1) What the claims as a whole cover

The determination of what the claims as a whole cover is first set forth for independent claim 62, and then for each of the other claims.

Claim 62 encompasses a protein comprising two parts: (a) a tumor necrosis factor (TNF)-binding soluble fragment of an insoluble TNF receptor with three recited characteristics (labeled (i), (ii) and (iii)); and (b) all of the domains of the constant region of a human immunoglobulin heavy chain other than the first domain of said constant region. Additionally, the protein of claim 62 must have the functional characteristic that it "specifically binds human TNF", which is provided by part (a). Possession of the protein of claim 62 necessarily entails possession of each of parts (a) and (b). Appellants possess the full scope of the genus of part (b) and it is not further considered herein (at pages 18-19 of the 2/28/08 Appeal Brief, Appellants state "[w]ritten description for the immunoglobulin portion of the fusion protein does not appear to be disputed").

Part (a) of claim 62 encompasses a soluble fragment that has a functional characteristic (human TNF-binding) and is also a fragment of an insoluble TNF receptor with three characteristics: (i) specifically binding human TNF, (ii) an apparent molecular weight of about 75 kilodaltons (kD) on a non-reducing SDS-polyacrylamide gel and (iii)

comprising amino acid sequence SEQ ID NO: 10. The specification teaches SEQ ID NO: 10 as peptide "IID" (page 8, lines 5-6) in a list of ten partial protein sequences starting at page 7, line 25, wherein it is shown as a sequence of 18 amino acids that includes 17 "known" residues and one "unknown" residue (position 8, labeled 'X'). The specification teaches (page 7, lines 22-25) that preferred proteins comprise at least one of the ten partial sequences, but does not teach any particular longer sequence from which SEQ ID NO: 10 is derived. The specification teaches that preferred proteins also have an apparent molecular weight of about "55 kD, 51 kD, 38 kD, 36 kD and 34 kD or 75 kD and 65 kD, especially those with about 55 kD and 75 kD" (page 7, lines 20-22). Example 7 of the specification teaches that SEQ ID NO: 10 was identified by NH_2-terminal sequencing of a 65 kD TNF-binding protein (page 33). The specification further teaches that "preferred DNA sequences which code for a protein of about 75/65 kD, whereby those which contain the partial cDNA sequences shown in Figure 4 are preferred" (page 10, lines 23-26). The amino acid sequence of SEQ ID NO: 4 is 392 amino acids, but does not include SEQ ID NO: 10. Thus, the "insoluble human TNF receptor" recited in claim 62 must bind to human TNF, have a weight of about 75 kD and include SEQ ID NO: 10, but may or may not include SEQ ID NO: 4.

Furthermore, the specification teaches that the invention concerns DNA sequences that encode non-soluble proteins that hybridize with the DNA sequence of Figure 4 (page 9, lines 22-24 and 34-37) and further teaches, "the present invention embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions, and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4" (page 10, lines 1-6) and "analogues of the sequences of Figure 4 "in which one or more amino acids have been replaced or deleted, without thereby eliminating TNF-binding ability" (page 5, lines 21-23). Thus, the insoluble receptor recited in the claims also encompasses variants with any number of mutations (including substitutions (replacements), deletions, and additions), as long as the resultant altered protein can bind to TNF, has an apparent weight of 75 kD on a non-reducing SDS polyacrylamide gel, and has the peptide sequence of SEQ ID NO: 10.

While the insoluble receptor referenced in the claims is required to have the three characteristics described above, the soluble fragment derived from this receptor is required to have just one of these characteristics: specifically binding to human tumor necrosis factor (TNF). The TNF-binding soluble fragment is not required to have any specific structural requirements with respect to sequence or molecular weight (i.e., the soluble fragment is not required to include the peptide SEQ ID NO: 10 or have a particular molecular weight). The requirement for being "soluble" is achieved by any fragment that does not include a transmembrane (cell-membrane spanning) region of an insoluble receptor. Thus, the genus of "soluble fragments" derived from an insoluble receptor includes any fragment including any fragment of the extracellular and/or the intracellular domains of the protein, ranging in size from each entire region to fragments as small as one amino acid residue. Further, as the specification envisions mutations (substitutions, deletions and additions) in the insoluble receptor, a "soluble fragment" can also include any of number of these mutations. From this genus of "soluble fragments", the claims are then limited to those particular fragments that can bind to the human TNF molecule.

The other claims included the rejection have the following scope.

Claims 105, 119, 120, 121, 123 and 124 each depend ultimately from claim 62 and have an identical scope with respect to part (a) of the claimed protein.

Claim 102 depends from claim 62 and requires the soluble fragment of part (a) to include two specific sequences: SEQ ID NO: 12 (peptide IIF on page 8 of the specification, which is 4 amino acids long and corresponds to residues 66-69 of SEQ ID NO: 4) and SEQ ID NO: 8 (peptide IIB on page 7 of the specification, which is also 4 amino acids long but is not found in SEQ ID NO: 4). The insoluble receptor must necessarily contain these sequences for them to be present in the soluble fragment, but the claims do not require them to be present in any particular position or order within the overall sequence. Independent claim 134 and dependent claim 136 have the same scope as claim 102 with respect to part (a) of the protein.

Claim 103 depends from claim 102 and further requires the soluble fragment of part (a) to include SEQ ID NO: 10; thus claim 103 requires that the soluble fragments

include a total of 25 specific amino acids (17 from SEQ ID NO: 10 and 4 from each of SEQ ID NO: 8 and 12). This represents the narrowest genus of soluble fragments recited in part (a) of any claim, however, the required peptides still only represent 25 amino acids of the 75 kD receptor, and can be present in any order or location within the sequence. Claim 135 depends from claim 134 and has the same scope as claim 103 with respect to part (a) of the protein.

Independent claim 106 requires the insoluble receptor of part (a) to have SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 8; SEQ ID NO: 9 (peptide IIC; which is 16 amino acids in length and corresponds to residues 276-291 of SEQ ID NO: 4) and SEQ ID NO: 13, peptide IIG which is 7 amino acids in length and corresponds to residues 230-236 of SEQ ID NO: 4). Each of SEQ ID NO: 9 and 13 is found in the intracellular domain of the naturally-occurring insoluble 75 kD TNF human receptor. This represents the narrowest genus of insoluble receptors recited in the claims, but still only requires 25 amino acids (from SEQ ID NOs: 10, 8 and 12) from the extracellular domain of the receptor, and of these, the recited soluble fragment requires only SEQ ID NO: 12 and SEQ ID NO: 8 (8 amino acids total). Claims 125-127 depend from claim 106 and have the same scope with respect to part (a). Claim 128 depends from claim 106 and requires that the soluble fragment of part (a) comprises SEQ ID NO: 10. As with claim 103, this represents the narrowest genus of soluble fragments recited in part (a) of any claim; however, the required peptides still only represent 25 amino acids of the 75 kD receptor and can be present in any order or location within the sequence.

Independent claim 107 requires that the insoluble receptor binds human TNF and has a weight of 75 kD and requires that the soluble fragment includes SEQ ID NO: 10; therefore the insoluble receptor must necessarily contain this sequence. Claims 129-132 depend from claim 107 and have the same scope with respect to part (a) of the protein. Claims 110 and 111 depend from 107 and further require the soluble fragment to include SEQ ID NO: 12 and 8. Claims 113 and 133 have same scope as claims 107, 110 or 111 with respect to part (a) of the protein.

Claim 114 is directed to a pharmaceutical composition comprising a protein of claim 62, 107, 134 or 135 and a pharmaceutically acceptable carrier. Claim 137 is

directed to a pharmaceutical composition comprising a protein of claim 105 a pharmaceutically acceptable carrier. Thus part (a) of the protein encompassed by claims 114 or 137 is the same as the parent claims from which they depend.

(2) Support for the claimed invention provided by Appellant

The specification provides the following support for the claimed invention.

The specification teaches a sample containing proteins having a weight of 75 kilodaltons (kD) and 65 kD (as determined by gel electrophoresis and Western blot) and that each "bonded TNF specifically in the filter test" (Example 4, in particular page 31, lines 9-22). Thus, the specification provides actual reduction to practice of an insoluble receptor 75 kD protein that can bind to human tumor necrosis factor (TNF). The specification does not teach the entire amino acid sequence of said protein and instead teaches only a partial sequence encoded by a partial cDNA sequence. The specification teaches identification of "75/65 kD TNB-BP-coding partial cDNA sequences" (Example 8, in particular page 35, lines 22-36) the only example of which is a cDNA sequence (SEQ ID NO: 3) encoding a protein sequence (SEQ ID NO: 4) (both shown in Figure 4) that is 392 amino acids long.

The specification further teaches (page 7, lines 22-25) that preferred non-soluble proteins of the invention include those comprising at least one of the ten "amino acid partial sequences" named IA, IB, IIA, IIB, IIC, IID, IIE, IIF, IIG and IIH (termed SEQ ID NOs 5-14; page 7, starting at line 13). Of these ten sequences, peptides IA and IB were identified by sequencing a 55kD TNF-binding protein (Example 7, starting at page 32, line 27); peptide IID (SEQ ID NO: 10) was identified by NH_2-terminal sequencing of the 65kD TNF-binding protein (Example 7, page 33, lines 7-19); and peptides IIA-IIC and IIE-IIH (SEQ ID NO: 7-9 and 11-14) are taught as "[a]dditional peptide sequences for 75(65)kDa-TNF-BP" (Example 7, page 33, starting at line 21). The reference to "75(65) kDa-TNF-BP" renders ambiguous whether each peptide was found with the 75 kD or the 65 kD protein or both. Thus, while the specification provides actual reduction to practice of a TNF-binding 65 kD protein comprising SEQ ID NO: 10, the specification does not provide actual reduction to practice of a TNF-binding 75 kD protein comprising

SEQ ID NO: 10, and is ambiguous as to the actual reduction of practice of a TNF-binding 75 kD or a 65 kD protein comprising SEQ ID NO: 5-9 and 11-14.

The specification further teaches that the invention includes soluble fragments of the non-soluble proteins that bind TNF (page 7, lines 13-16). Peptides IIA-IIH themselves represent soluble fragments that were identified from partial sequences of a 65 kD or 75 kD receptor (see above); however, none of these fragments is taught as being able to bind TNF by themselves. The specification does not teach any other soluble fragments that can bind to TNF. Therefore, the specification does not provide actual reduction to practice of a TNF-binding soluble fragment of any human TNF-binding 75 kD insoluble receptor. Furthermore, while the specification indicates that the insoluble receptor should include at least one of peptides IIA-IIH, the specification does not teach that the soluble fragments should include any particular sequences, or any particular sequences of the 75 kD receptor that are required for binding.

The specification also teaches that "peptides IIA, IIC, IIE, IIF, IIG and IIH are coded by the partial cDNA sequence in Figure 4" (page 10, lines 28-29). The specification does not teach any particular longer sequence from which peptide IID (SEQ ID NO: 10) is derived. Thus, the specification teaches actual reduction to practice of a partial cDNA sequence (SEQ ID NO: 3) encoding a protein sequence (SEQ ID NO: 4) with shared amino acid sequences with some of the identified soluble fragment sequences. The specification does not teach whether or not the protein sequence of SEQ ID NO: 4 can bind to human TNF, but repeatedly refers to TNF-binding fragments and variants of SEQ ID NO: 4. On page 3, the "Summary of the Invention" states, "This invention also comprises TNF-binding proteins containing amino acid sequences of Figure 1 or Figure 4, proteins containing fragments of these sequences, and proteins analagous [sic] to the sequence of Figure 1 or Figure 4 or to fragments thereof" (page 3, lines 25-29). Thus, the specification points the skilled artisan to fragments of Figure 4 and not fragments of the full-length TNF-binding 75 kD insoluble receptor. On page 5 the "Detailed Description of the Invention" states that "[t]he TNF-binding proteins of the present invention include homogenous proteins containing the amino acid sequence depicted in Figure 1 or in Figure 4, proteins containing fragments of either sequence,

and analogs of any such proteins for example proteins containing amino acid sequence analogous to the amino acid sequences of Figure 1 or Figure 4 or to fragments thereof. An analogue is a protein in which one or more amino acids of the sequence depicted in Figure 1 or in Figure 4 have had their side-groups chemically modified in a known manner, or those in which one or more amino acids have been replaced or deleted, without thereby eliminating TNF-binding ability" (page 5, lines 11-24). The phrase "without thereby eliminating TNF-binding ability" implies that the sequence of Figure 4 has TNF-binding ability, however this is not actually tested for this sequence.

The specification does not describe actual reduction to practice of a fusion protein comprising a human TNF-binding soluble fragment of a human TNF-binding 75 kD insoluble receptor. The specification does not teach actual reduction to practice of any human TNF-binding 75 kD insoluble receptors envisioned by the specification encoded by "DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4…" (page 10, lines 2-4), or any soluble fragments derived from such variants.

The specification teaches that the "TNF binding activity of the proteins of the present invention may be determined using the assay described in Example 1" (page 5, lines 27-29). The specification does not teach that any soluble fragments of a 75 kD TNF-binding insoluble receptor were tested using this assay, nor does the specification teach what results would be expected in this assay with any particular soluble fragment.

(3) Whether one skilled in the art would recognize that the Appellant was in possession of the claimed invention as a whole.

The determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing includes the following considerations: (a) actual reduction to practice; (b) disclosure of drawings or structural chemical formulas; (c) sufficient relevant identifying characteristics such as complete or partial structure(s); physical and/or chemical properties; and/or functional characteristics when coupled with a known or disclosed

correlation between function and structure; (d) method of making the claimed invention; (e) level of skill and knowledge in the art; and (f) predictability in the art.

The actual reduction to practice, structural chemical formulas (sequences), relevant identifying characteristics, functional characteristics and method of making the claimed invention disclosed in the instant specification are described above.

As described above, claim 62 is directed to those "human TNF-binding" species within a genus of "soluble fragments" derived from the insoluble receptor that binds to human TNF, have a weight of about 75 kD and include SEQ ID NO: 10. The genus of "soluble fragments" from which to select TNF-binding species includes any fragment including any portion of the extracellular and/or the intracellular domains of the receptor, ranging in size from each entire region to fragments as small as one amino acid residue. Furthermore, as the specification envisions mutations (substitutions (replacements), deletions and additions) in the insoluble receptor, the genus of "soluble fragments" can also include any of number of these mutations. This genus is vast even if considering only soluble fragments derived from the extracellular domain of the naturally-occurring 75 kD receptor. As described below, the extracellular domain (ECD) of the naturally-occurring 75 kD receptor is 235 amino acids in length, and thus "soluble fragments" includes fragments of the ECD ranging from 1 to 235 amino acids in length, and the potential mutants include mutations at one or more of 235 positions. From this vast genus of "soluble fragments", the claims are then limited to those particular fragments that can bind to the human TNF molecule. However, while the specification teaches that the invention includes human TNF-binding soluble fragments of a human TNF-binding 75 kilodalton (kD) receptor, it does not teach any particular sequences constituting such a human TNF-binding soluble fragment. As stated in MPEP 2162, "[i]nformation which is well known in the art need not be described in detail in the specification". However, at the time of the effective filing date merited for the claimed protein, there was no particular human TNF-binding soluble fragment of a human TNF-binding 75 kilodalton (kD) insoluble receptor that was well known in the art.

Two prior art references (each published before the effective priority date merited for the claimed protein (8/31/90); see page 2 of the 10/9/07 Advisory Action) disclose

the complete amino acid sequence of a human TNF-binding 75 kilodalton (kD) insoluble receptor comprising a sequence encompassed by SEQ ID NO: 10. The references (each of record in the prosecution of the instant application) are Smith (May 25 1990. Science. 248: 1019-1023; page B-211 of the Appeal Brief), which describes such a sequence at page 1021 (Figure 4) and Dembic (July 1990. Cytokine 2(4): 231-7; page B-80 of the Appeal Brief), which describes such a sequence at page 232 (Figure 1). In Figure 1 (page 232), Dembic teaches a human TNF-binding 75 kD insoluble receptor in which 17 of the first 18 amino acids are identical to instant SEQ ID NO: 10 (the other amino acid corresponds to the "unknown" residue at position 8 of SEQ ID NO: 10). This receptor is 439 amino acids in length, including an extracellular region (amino acid residues 1-235), a transmembrane region (residues 236-260; double-underlined in Figure 1 of Dembic), and an intracellular domain (residues 261-439). The relatively short transmembrane region (25 amino acids) confers on the receptor the functional characteristic of being "insoluble"; that is, this region tethers the full-length receptor to the cell-membrane, rendering it insoluble in water. Smith discloses the same sequence in Figure 3 (page 1021), but with the addition of 22 amino acids at the start of the protein, which is a signal sequence not present in the mature expressed protein.

Dembic teaches that a naturally-occurring soluble TNF-binding protein exists in human serum and has an NH_2-terminal sequence that matches a sequence starting with the fifth amino acid of the full-length 75 kD insoluble receptor (left column of page 235). Dembic further teaches that this soluble protein is "presumably of the extracellular region" of the receptor (page 235). Dembic does not teach that size of this soluble protein or indicate how much of the extracellular region it comprises. Thus, the sequence of this soluble protein cannot be considered to be well-known in the art.

Dembic further teaches a "schematic representation" of the 235-amino acid extracellular region of the 75 kD insoluble receptor, which includes four domains of cysteine rich repeats (residues 17-54, 55-97, 98-140 and 141-179; Figure 2, page 233). Dembic does not teach which residues in the extracellular region are required for TNF-binding. Smith (1990) teaches that, "[t]he NH_2-terminal 162 amino acids (positions 39 to 200) are rich in cysteines (22 residues)..." (pages 1020-1021) and "[t]he net charge

associated with the cysteine-rich domains of these family members varies ... which may be related to ligand specificity. Presumably, it is this NH_2-terminal region that contains the TNF binding site" (page 1021). Residues 39-200 taught by Smith include the leader signal sequence in their numbering and correspond to residues 18-179 as taught by Dembic. Thus, while Dembic and Smith generally teach that the TNF-binding region of the insoluble receptor is found in particular regions of the extracellular domain, they do not teach a soluble fragment that can bind to human TNF.

Therefore, the sequence of a human-TNF binding soluble fragment of the 75 kD insoluble TNF receptor could not have been considered to have been well-known in the art at the time of filing. Therefore, the written description of the genus of human-TNF binding soluble fragments encompassed by the claims requires a detailed description in the specification of the instant application. As described above (in section (2)), the instant specification does not provide an actual reduction to practice of any members of said genus. The specification is silent as to whether any of the sequences disclosed as important to the invention, such as the protein (SEQ ID NO: 4) encoded by the partial cDNA sequence of the 75 kD TNF receptor or the identified soluble fragments (peptides IIA-IIF, also known as SEQ ID NO: 7-14) have the ability to bind to TNF. Furthermore, there is no teaching in the instant specification of any particular species of "soluble fragment" of a 75 kD receptor with TNF binding activity. There is no teaching in the specification identifying either the entire extracellular region of the 75 kD TNF receptor, or any particular portion of this region, as important to TNF-binding. There is no teaching in the instant specification that the entire extracellular domain of the naturally-occurring 75 kD TNF receptor is a desired portion of the receptor to be used in the fusion protein. There are no teachings in the instant specification regarding use of the extracellular domain of 75 kD TNF receptor. Instead the specification only refers to a genus of soluble fragment derived from a genus of 75 kD insoluble TNF receptors, and only refers to partial sequences of the protein (SEQ ID NO: 4-14) and fragments of said partial sequence – despite the fact that the full-length protein sequence was already known in the art.

While the instant specification does not teach such, a comparison by the skilled artisan at the time of filing of SEQ ID NO: 4 with the receptor sequences taught by Dembic and Smith would have shown that the protein (SEQ ID NO: 4) encoded by the "partial cDNA" sequence consists only of residues 49-439 of the full-length receptor taught by Dembic. Chan (2000, Science, 288: 2351-2354; cited previously) provides teachings regarding the required binding domains of both the 55 kD and the 75 kD insoluble TNF-binding receptors. Specifically, Chan teaches that "[t]he ligand-binding pocket for TNF-α is mainly formed by CRD2 [cysteine-rich domain 2] and CRD3 [cysteine-rich domain 3] of the TNFRs", which are residues 55-97 and 98-140 (as taught by Dembic). However, Chan also teaches "[t]he deletion of PLAD [protein-ligand assembly domain] from either p60 or p80 completely abrogated ligand binding (Table 1 and Fig. 1E)" (page 2351; Chan refers to the 55 kD TNF receptor as "p60" and the 75 kD TNF receptor as "p80"). Chan teaches that the PLAD of the 75 kD receptor is amino acids 10-54 and "is physically distinct from the ligand contact domain but nonetheless essential for efficient TNF-α binding and receptor function" (page 2351). Thus, the teachings of Chan indicate that the sequence of SEQ ID NO: 4 does not contain sufficient residues to bind to TNF. Thus, any fragment generated from SEQ ID NO: 4 would correspondingly not have the ability to bind to TNF. Nowhere does the specification contemplate a particular soluble fragment including critical residues 10-54 (as evidenced by Chan (2000)) as a particular species of the invention. Thus, Appellants do not specifically point to any particular species of soluble fragment that can actually bind TNF with the genus of claimed soluble fragments.

Peptides IIA-IID and IIF-IIH (SEQ ID NO: 7-10 and 12-14, page 7, starting at line 32) represent the following amino acids found in the 75 kD sequence taught by Dembic: 1-7 and 9-18 (IID, SEQ ID NO: 10); 43-47 (IIB, SEQ ID NO: 8); 66-69 (IIF, SEQ ID NO: 12); 278-284 (IIG, SEQ ID NO: 13); 288-302 (IIH, SEQ ID NO: 14); 324-339 (IIC, SEQ ID NO: 9); and 421-435 (IIA, SEQ ID NO: 7). Peptide IIE (SEQ ID NO: 11) is taught to have been identified from the 65 kD or 75 kD protein, but an exact match is not found in the sequence taught by Dembic (residues 123-128 match 5 of the 13 residues of IIE). However, while the specification teaches these soluble fragments, it does not teach

whether or not any of them can bind to TNF. However, IIG, IIH, IIC, IIE and IIA are in the intracellular domain on the inside of the cell and therefore could not bind to the extracellular TNF ligand. Furthermore, the post-filing date art teaches that the "soluble fragments" of IID (SEQ ID NO: 10), IIB (SEQ ID NO: 8) and IIF (SEQ ID NO: 12) could also not bind TNF. In particular, U.S. Patent 5,395,760 (Smith et al, 3-1995; page B-219 of the of the 2/28/08 Appeal Brief) shows that a truncation to residues 1-142 destroys TNF binding activity, and thus smaller fragments such as IID, IIB and IIF also could not bind TNF. Even the combination of all of these sequences would not be sufficient to provide TNF binding. Therefore, the recitation of these sequences in one or more of the claims does not provide sufficient structure to provide TNF binding for either the insoluble receptor or soluble fragments thereof. Even the narrowest of soluble fragments recited in part (a) of claim 128 only requires a total of 25 specific residues, (17 from SEQ ID NO: 10, 4 from SEQ ID NO: 12, 4 from SEQ ID NO: 8) of the extracellular domain of receptor (out of 235 amino acids). Thus, the claims still encompass variants in one or more of 235 positions in the extracellular domain, and the specification does not teach the sequences required for TNF binding.

The instant specification also provides a single reference to Smith (1990) on page 10, lines 9-10 which states "[o]ne sequence which results from such a deletion is described, for example, in Science 248, 1019-1023, (1990)". However, the only reference to "deletions" in the immediate previous sentence is to deletions from the sequence of Figure 4. Any deletion to the sequence of Figure 4 would also result in a protein that could not bind TNF. Thus, this reference to Smith cannot provide a description of TNF-binding soluble fragments.

Chan (2000) further shows experimentally that some specific single or double mutations in the PLAD region of the 55 kD receptor eliminate TNF binding whereas others do not. Specifically, mutation of residues 19 and 20 (double mutation); 32 (single); 57 (single); or 66 (single) eliminate TNF binding, whereas mutation of residues 19 (single); 24 (single); 49 and 50 (double); 61 (single), 77 (single), 108 (single) or 112 (single) do not. Chan teaches a high degree of structural similarity between the extracellular region of the 55 kD and 75 kD receptor, indicating that the TNF-binding site

of the 75 kD receptor would be similarly sensitive or insensitive to particular single or double substitution mutations. The teachings of Chan provide evidence that the scope of the genus of "(TNF)-binding soluble fragments" of a TNF-binding 75 kD insoluble receptor (as encompassed by claim 62) is not limited to a single species (e.g., a non-mutated extracellular domain of the receptor) but instead includes an unknown number of species that have one or more mutations in the extracellular domain but that retain TNF binding. Thus, post-filing date art provides evidence that while some mutations can be made to the extracellular domain and retain TNF binding, other mutations result in loss of TNF binding. As such, the post-filing date art provides evidence that it would have been unpredictable in the art at the time of filing as to which mutations could be made to the 75 kD insoluble receptor and retain TNF binding. Thus, the level of predictability in generating TNF-binding soluble fragments of mutated receptors is low.

Thus, the specification envisions a genus of TNF-binding soluble fragments, yet does not teach any particular species of TNF-binding soluble fragment of the 75 kD TNF-binding insoluble receptor. Neither the partial receptor sequence (SEQ ID NO: 4) taught by the specification, nor the soluble fragments taught by the specification, actually has the ability to bind to TNF. With respect to the level of skill, knowledge and predictability in the art, an important consideration is that structure is not necessarily a reliable indicator of function. In the instant specification, there is no disclosure relating similarity of the variable structure of the soluble fragments to conservation of function. General knowledge in the art at the time of filing included the knowledge that some amino acid variations are tolerated without losing a protein's tertiary structure. However, conservation of structure is not necessarily a surrogate for conservation of function. The post-filing art of Chan (2000) provides evidence that some amino acids of the extracellular domain are required for TNF-binding, yet others can be mutated without loss of activity. The specification fails to provide sufficient descriptive information of a disclosed correlation between structure of the soluble fragments and the function of TNF-binding. Even if the specification did teach a particular species of TNF-binding soluble receptor, this would not be sufficient to support the scope of the claimed variants, which include any number of mutations (substitutions, additions and/or

deletions) and yet must retain TNF binding. No correlation is provided between particular mutations and the functionality of TNF binding. Thus, the specification does not reasonably convey to those skilled in the art that applicant was in possession of even a single species of soluble fragment that can bind to TNF, let alone a representative number of species of the genus of TNF-binding soluble fragments encompassed by the claims.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Appellants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure (amino acid sequence) of the encompassed genus of TNF-binding soluble fragments comprised by the claimed protein and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the instant claims do not meet the written description provision of 35 U.S.C. §112, first paragraph. *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121, 125-131 and 134-137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dembic et al (July 1990. Cytokine 2(4): 231-7) in view of Capon et al, U.S. Patent No. 5,116,964 (published 5/26/92 and filed 11/22/89).

Claims 62, 102, 103, 105-107, 110, 111, 113, 119-121, 125-131 and 134-136 each encompass a genus of proteins. While the scope varies, each genus encompasses the following: a purified protein recombinantly produced in CHO cells that specifically binds human TNF and consists of parts (a) and (b). Part (a) of each claim encompasses a TNF-binding soluble fragment including SEQ ID NO: 10, 8 and 12 of an insoluble human TNF receptor; wherein said receptor has three characteristics: (i) specifically binds human TNF; (ii) molecular weight of about 75 kD; and (iii) comprises SEQ ID NO: 10, 8, 12, 13 and 9. Part (b) of each claim encompasses "all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain of said constant region". The narrowest claims limit immunoglobulin heavy chain to human IgG_1; however, all of the claims encompass this limitation.

Dembic teaches the amino acid sequence of a TNF-binding 75 kD insoluble receptor, including the 235 residues of the extracellular domain (Figure 1 on page 232). This insoluble (membrane-bound) receptor has the three characteristics described above: (i) it binds human TNF; (ii) has a molecular weight of about 75 kD; and (iii) comprises the following sequences: SEQ ID NO: 10 (LPAQVAFXPYAPEPGSTC; residues 1-18 of Figure 1); SEQ ID NO: 8 (VFCT; residues 43-47); SEQ ID NO: 12

(LCAP; residues 114-117) and SEQ ID NO: 13 (VPHLPAD; residues 278-284); and SEQ ID NO: 9 (NQPQAPGVEASGAGEA; residues 323-340). Dembic further teaches that a naturally-occurring TNF-binding peptide found in human serum is a soluble fragment that presumably consists of "the extracellular regions" of the 75 kD TNF receptor (see page 235, column 1). Dembic does not teach a fusion of the extracellular domain of the 75 kD TNF receptor with a portion of the constant region of a human IgG_1 immunoglobulin heavy chain.

Capon teaches hybrid immunoglobulins comprising the extracellular domain of a membrane bound receptor, both generally and with a specific example (Example 4, starting at column 40) wherein truncated murine lymphocyte homing receptor (MHLR) extracellular domain is fused to the Fc region of human IgG_1 (“These truncated proteins are all joined to a human heavy chain γ 1 region just upstream of the hinge domain (H) such that these chimeras contains the two cysteine residues of the hinge responsible for dimerization as well as the CH2 and CH3 constant regions.”) Capon teaches that the "boundary for the LHR extracellular domain generally is at, or within about 30 residues of, the N-terminus [NH_2-terminus] of the transmembrane domain, and is readily identified from an inspection of the LHR sequence" (column 9, lines 22-26). The Fc region consists of the CH2 and CH3 domains of the constant region but does not include the CH1 domain. Capon further teaches that hybrid immunoglobulins can be used for affinity purification of ligands (column 22, lines 5-6). Capon further teaches recombinant production of hybrid immunoglobulins in cell culture (column 26, lines 24-26). Capon further teaches that CHO cells are suitable eukaryotic cells for production of hybrid immunoglobulins (column 29, line 37). Capon further teaches purification of the hybrid immunoglobulin from cell cultures following expression in host cells (column 30, line 26-27). Capon further teaches placement of the purified hybrid immunoglobulin in “sterile, isotonic formulations” that are “preferably liquid” and “ordinarily a physiologic salt solution” (column 31, lines 4-8). Such solutions meet the definition of a “pharmaceutically acceptable carrier material” (as in claim 114).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to fuse the extracellular portion of the 75 kD human TNF receptor

sequence taught by Dembic to the Fc region taught by Capon, and to recombinantly produce the protein in CHO cells and purify the protein produced as taught by Capon. The person of ordinary skill in the art would be motivated to do so in order to produce and purify the TNF receptor-Ig fusion for use in affinity purification of the TNF ligand. The person of ordinary skill in the art would have expected success because Capon teaches that Ig fusions can be made with a wide variety of proteins, and teaches all of the techniques for recombinant production of hybrid immunoglobulins in CHO cells and purification of the produced protein.

With respect to claims 114 and 137, the recitation of "a pharmaceutical composition" in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight. Therefore, the claims encompass any composition comprising a recombinant protein of claims 62, 107, 134 or 135 (claim 114) or claim 105 (claim 137) and a pharmaceutically acceptable carrier material. As described above, Capon teaches compositions comprising a hybrid immunoglobulin in a pharmaceutically acceptable carrier material. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to further include the hybrid TNF receptor-immunoglobulin in a pharmaceutically acceptable carrier material. The person of ordinary skill in the art would be motivated to do so in order to resuspend the hybrid immunoglobulin for use following purification. The person of ordinary skill in the art would have expected success because Capon teaches the necessary procedures for purification and resuspension of the hybrid immunoglobulin.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 140-144 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claim 140 is directed to a protein comprising the "human tumor necrosis factor (TNF) binding soluble fragment of the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC on October 17, 2006 under accession number PTA 7942". The "Third Declaration of Dr. Werner Lesslauer under 35 U.S.C. § 1.132" submitted 11/14/06 states that the "DNA construct designated N227 containing DNA sequence which includes sequence encoding the signal sequence and the extracellular domain of human p75 tumor necrosis factor receptor (TNFR) was constructed on a date before September 10, 1990" and the "DNA sequence within construct N227 is a DNA sequence identified in the above referenced application at page 10, line 34". Appellants' 11/14/06 amendments to the specification at page 10 introduce deposit information to the following sentence: "DNA sequences which code for insoluble (deposited on October 17, 2006 with the American Type Culture Collection under Accession No. PTA 7942) as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred" [the underlined portion represents the material added to the specification].

The claims indicate that the plasmid deposited with the ATCC contains a cDNA insert. The only cDNA insert in the specification related to the 65 kD/75 kD TNF-binding protein is the partial cDNA sequence (SEQ ID NO: 3) shown in Figure 4 that encodes a protein of SEQ ID NO: 4. This cDNA sequence does not contain a signal sequence and is missing part of the sequence encoding the extracellular domain required for TNF binding. While the description added to the specification does not clearly indicate what DNA sequence was deposited, it appears that Appellants have deposited a plasmid containing a DNA sequence including a signal sequence, such as DNA encoding the full-length 75 kD insoluble human TNF receptor. However, there is no support in the specification at the time of filing for a cDNA insert encoding the full-length extracellular domain of 75 kD TNF receptor, and no support in the specification at the time of filing for a cDNA insert encoding a TNF-binding soluble fragment.

Furthermore, there is no clear description in the specification as originally filed for the specific DNA construct designated N227. There is no conception of the specific construct, nor does the concept of the specific construct flow naturally from the

disclosure of the specification. As noted above, Appellants have amended the specification to include reference to the deposit after the word "insoluble" in a sentence that originally read, "DNA sequences that code for insoluble as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred". However, the original teaching in the specification is directed to a genus of "DNA sequences that code for insoluble … fractions of TNF-binding proteins having an apparent molecule weight of 65 kD/75 kD" and does not teach the particular species of construct deposited and claimed by Appellants.

Therefore, the specification as originally filed lacks support for the proteins encompassed by the claim 140. Claims 141-144 are included in this rejection because they depend from claim 140 and encompass the same new matter.

Withdrawn Claim Rejections

35 USC § 112, 1st paragraph, enablement

On further consideration the rejection of the claims 140-144 under 35 U.S.C. § 112, first paragraph, for lack of enablement is *withdrawn*. This rejection was set forth in the 2/23/2007 Final Rejection and was necessitated by the addition of new claims 140-144, which employ novel biological materials and reference a biological deposit that at the time did not meet the requirements for deposit. The rejection also stated that the deposit did not meet the requirements of 37 C.F.R. § 1.809(d)(3) because the specification did not contain a specific description of the deposited biological material sufficient to specifically identify it and permit examination. Appellants subsequently filed a "Declaration of Biological Culture Deposit Under Terms of the Budapest Treaty" on 8/6/2007, which was held sufficient (in the Advisory Action mailed 10/19/07) to indicate the deposit was made under terms of the Budapest treaty and all restrictions imposed by the depositor on availability will be removed upon granting of a patent. However, the rejection was maintained on the grounds that the deposit still did not meet the requirements of 37 C.F.R. § 1.809(d)(3). On further consideration, the amendments to the specification (containing a reference to accession number PTA 7942) do contain a sufficient description to specifically identify the deposited biological material and permit

examination. Therefore, the enablement rejection of claims 140-144 is withdrawn. However, the rejection of claims 140-144 for containing new matter is maintained for the reasons set forth previously and reiterated herein (see above).

(10) Response to Argument

Appellants' arguments (pages 11-66 of the Appeal Brief filed on 2/28/08) are addressed by section in the order presented by Appellants.

Brief Description of Invention, Background and Specification **(pg 11-16)**

Appellants' "Brief description of Invention, Background and Specification" has been fully considered. No particular statements are disputed. However, the following is noted. At page 11, Appellants state, "TNF-binding soluble fragments of p75 TNFR include the extracellular domain and TNF-binding portions thereof". While it is true that an isolated extracellular domain of a TNF binding 75 kilodalton (kD) insoluble receptor (here called "p75 TNFR") is a soluble fragment that would bind to human TNF, and is encompassed by the TNF-binding soluble fragment recited in the claims, nowhere does the specification describe such an isolated extracellular domain, or a particular TNF-binding portion thereof, or indicate that this particular species is a specific embodiment of the genus of TNF-binding soluble fragments encompassed by the claims.

A. The written description rejection of claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121 and 123-137 under 35 USC § 112, 1st paragraph (pg 16-39).

In this section, Appellants first provide a "Brief Statement of the Relevant Prosecution History" (pages 16-18). Appellants' statements regarding the prosecution history have been fully considered and none are disputed. Appellants then advance arguments, divided by groupings of claims, why the rejection should be reversed (pages 18-39), and are addressed in the order presented in the Appeal Brief.

1. The written description rejection of claims 62, 102, 103, 105, 107, 110, 111, 113, 114, 119, 120, 123, 124, 129, 130, 132, 133 and 137 (pg 18-34).

a. Appellants' argument they actually possessed and adequately described TNF binding proteins comprising the full length extracellular domain (pg 18-21).

In this section, Appellants present the following arguments. Appellants argue that the rejection insists that the application only describes soluble fragments of the sequence of Figure 4, which is missing amino acids 1-48 of the 75 kilodalton (kD) receptor (here called the "p75 TNFR"), but that this position disregards embodiments that Appellants actually possessed and exemplified and fails to consider what the specification reasonably conveys to the skilled artisan. Appellants argue that written description does not require literal support, but merely that applicants reasonably convey to one of skill in the art that they were in possession of the invention at the time of filing; in support, Appellants point to *Vas-Cath Inc. v. Mahurkar* (1991). Appellants set forth six arguments ((a)-(f)) why the specification adequately describes to a skilled artisan human TNF-binding soluble fragments of a 75 kD insoluble TNF receptor.

These arguments have been fully considered but are not found to be persuasive. The rejection did not disregard embodiments of the invention that Appellants actually possessed and exemplified, and fully considered what the specification reasonably conveys to the skilled artisan. The Examiner does not dispute Appellants' characterization of *Vas-Cath*; however, for the reasons set forth in the rejection, the specification as filed does not reasonably convey to one of skill in the art that Appellants were in possession of the claimed invention at the time of filing. Each of Appellants' six arguments (labeled (a)-(f)) as to why the specification adequately describes TNF-binding soluble fragments are addressed in turn.

The Examiner does not dispute the statements in part (a) on page 19. The data in Examples 4-7 shows that Appellants possessed a sample that contains a human TNF-binding insoluble receptor, which based on its weight of about 75 kD presumably included a full-length extracellular region. However, as noted in the rejection the specification does not teach an isolated, full-length extracellular domain of this protein as a particular species of the invention, or even teach that the full-length extracellular domain is an important or critical part of the TNF-binding soluble fragments.

In part (b) on pages 19-20, Appellants argue that the specification contemplates soluble and insoluble fragments of the full-length purified p75 TNFR, and that it is therefore wholly unreasonable for the Examiner to insist that the description of Appellants' invention must be limited to less than actually possessed and exemplified. This argument has been fully considered but is not found to be persuasive. The Examiner does not dispute that the specification contemplates soluble and insoluble fragments of the human TNF-binding 75 kD insoluble receptor. However, contemplation of a genus of human TNF-binding soluble fragments of an insoluble receptor does not indicate that Appellants actually possessed the claimed genus.

In part (c) on page 20, Appellants argue that the teachings at page 14, lines 32-36 and the partial cDNA sequence of Figure 4 would have led the skilled artisan to Smith (1990). This argument has been fully considered but is not found to be persuasive. The Examiner disputes Appellants' interpretation of the quoted sentence. The sentence on page 14, lines 32-36 states that "On the basis of the thus determined sequence and of the already known sequences for certain receptors, those partial sequences which code for soluble TNF-BP fragments can be determined and cut out from the complete sequence using known methods [42]". The paragraph from which this sentence is taken describes using the sequences of "Figure 1 as well as Figure 4" to design oligonucleotides to probe cDNA or genome banks for related sequences (see page 42, lines 6-15 and lines 27-30). Thus, in context the phrase "thus determined sequence" refers to a hypothetical newly identified sequence from a cDNA or genome bank and "already known sequences" refers to the sequences of Figure 1 or 4. Reference "[42]" in the quoted sentence is identified on page 46 as Sambrook (1989) which is a general text describing molecular cloning techniques, and which does not teach any "already known sequences" that bind TNF. Thus, there is no reference in the paragraph to any other "already known sequences" such as Smith (1990), and is nothing leading the skilled artisan from this paragraph back four pages to the single reference to the Smith (1990) on page 10, line 10 of the specification. Appellants further argue that the Lyman Declaration at paragraph 16 provides evidence that it would be clear to the skilled artisan that the protein sequence shown in Figure 4 is the same as

the one described in Smith. While the Lyman Declaration provides evidence that at the time of filing one of skill in the art would look to publications in the prior art to complete the sequences of partial cDNAs, this evidence is not sufficient to overcome the rejection because even if the skilled artisan recognized that Figure 4 is a partial sequence of the sequence taught in Smith, there is still nothing in the instant specification contemplating particular use of the full-length extracellular domain as a soluble fragment in the claimed protein. Furthermore, even if Appellants possessed a soluble fragment consisting of the entire extracellular domain of the 75 kD receptor, possession of this single species does not provide a written description of the large genus of TNF-binding soluble fragments (including variants with one or more mutations) encompassed by the claims.

In part (d) at page 20, Appellants argue that the specification directs the reader to where "already known sequences" can be found by citing Smith (1990). This argument has been fully considered but is not found to be persuasive. As described above, the use of "already known sequences" on page 14 is not connected to the reference of Smith, which is cited on page 10 solely in reference to deletions from the sequences of Figure 4. As set forth in the rejection, there is a single reference to Smith (1990) on page 10, lines 9-10 which states "[o]ne sequence which results from such a deletion is described, for example, in Science 248, 1019-1023, (1990)". However, the only reference to "deletions" in the immediate previous sentence on page 10 is to deletions from the sequence of Figure 4. Any deletion to the sequence of Figure 4 would also result in a protein that could not bind TNF. Thus, this reference to Smith cannot provide a description of TNF-binding soluble fragments.

In part (e) on page 20, Appellants argue that Example 11 in the specification, which describes a fusion protein containing the extracellular domain of the 55 kD TNFR fused to all of the domains of an IgG heavy chain constant region other than CH1, applies equally to the 75 kD TNFR receptor because the specification teaches that both 55 kD and 75 kD are preferred embodiments and that describe examples are stated to not be limiting. This argument has been fully considered but is not found to be persuasive. While the specification on page 20 indicates that the specific examples are not intended to be limiting, there is no teaching in the specification that the teachings

with respect to the 55 kD receptor can be applied to "TNF-binding proteins" in general. Furthermore, there is no description of how to select a "human TNF-binding soluble fragment" that can be applied to the genus of "TNF binding proteins" that include both the 55 kD and the 75 kD insoluble receptor. In the instant specification, Example 11 does indicate that "the extracellular region of the 55 kD TNF-BP" was used to construct an immunoglobulin fusion protein. However, there is no teaching that this "extracellular domain" is a TNF-binding fragment and there is no teaching in the specification indicating that a similar region should be used with the TNF-binding 75 kD insoluble receptor, or with TNF-binding insoluble receptors in general. Furthermore, the specification generally teaches away from using the entire extracellular domain of the 75 kD receptor as a species of soluble fragment. First, while the full-length 75 kD TNF receptor was known in the art, the application when discussing the invention repeatedly refers to a partial sequence encoded by SEQ ID NO: 4, and fragments thereof. On page 3, the "Summary of the Invention" states, "This invention also comprises TNF-binding proteins containing amino acid sequences of Figure 1 or Figure 4, proteins containing fragments of these sequences, and proteins analagous [sic] to the sequence of Figure 1 or Figure 4 or to fragments thereof" (page 3, lines 25-29). Thus, the specification points the skilled artisan to fragments of Figure 4 and not fragments of the full-length TNF-binding 75 kD insoluble receptor. On page 5 the "Detailed Description of the Invention" states that "[t]he TNF-binding proteins of the present invention include homogenous proteins containing the amino acid sequence depicted in Figure 1 or in Figure 4, proteins containing fragments of either sequence, and analogs of any such proteins for example proteins containing amino acid sequence analogous to the amino acid sequences of Figure 1 or Figure 4 or to fragments thereof. An analogue is a protein in which one or more amino acids of the sequence depicted in Figure 1 or in Figure 4 have had their side-groups chemically modified in a known manner, or those in which one or more amino acids have been replaced or deleted, without thereby eliminating TNF-binding ability" (page 5, lines 11-24). The phrase "without thereby eliminating TNF-binding ability" implies that the sequence of Figure 4 has TNF-binding ability. However, Figure 4 depicts a partial amino acid sequence starting at residue 49 of the mature 75

kD TNF receptor as taught by Smith (1990) and Dembic (1990), and thus missing a portion of critical residues 10-54 identified by Chan (2000). Thus, while the specification implies that SEQ ID NO: 4 has TNF-binding ability, the art shows that the sequence of Figure 4 does not have TNF-binding ability.

The only cDNA in the specification related to 75 kD receptor (SEQ ID NO: 3) is shown in Figure 4. Thus, even if the teachings of Example 11 were applied to the 75 kD receptor, it would only result in amplification of a cDNA encoding a protein with a partial extracellular domain of the 75 kD receptor, which as shown by the post-filing art (Chan, 2000) would not bind TNF. The specification does not contemplate use of the full-length extracellular domain of a 75 kD TNF-binding insoluble receptor, and in fact teaches away from this particular species as described above.

In part (f) on pages 20-21, Appellants argue that the prior art of Dembic (1990), co-authored by inventors of the application, shows that the inventors in fact possessed the full-length amino acid sequence of mature human p75 prior to the instant application's filing date. This argument has been fully considered but is not found to be persuasive. As stated above with regard to argument (a), the Examiner does not dispute that Appellants were in possession of a human TNF-binding 75 kD insoluble TNF receptor. Furthermore, it is not disputed that the entire sequence of the 75 kD receptor was known in the art (e.g., Dembic, 1990). However, the specification does not indicate that the full-length extracellular domain of this protein is to be used as a particular TNF-binding soluble fragment of the claimed protein. Thus, the specification does not provide a written description of this particular species.

b. Appellants' argument that the Examiner erred in disregarding controlling case law in factually parallel cases (pg 21-24).

In this section, Appellants argue that the rejection relies on the absence of the entire sequence of the 75 kilodalton (kD) insoluble human TNF receptor in the specification, but that this is a legal error because the entire sequence was known in the art. Appellants argue that the Examiner "erred in disregarding controlling case law in factually parallel cases, which each held that the specification need not reproduce DNA

sequences that were already known in the art to satisfy the written description requirement". Appellants point to *Monsanto v Scruggs* (2006) and discuss *Capon v Eshhar* and *Falkner v Inglis* (2006) in detail on pages 21-24.

These arguments have been fully considered but are not found to be persuasive. The instant claims are not rejected because the specification fails to reproduce the full-length sequence of human TNF-binding 75 kD insoluble receptor taught in the prior art, but are instead rejected because the claims encompass a genus of human TNF-binding soluble fragments and the specifications fails to describe this genus. With respect to a species consisting of the full-length extracellular domain of the receptor, the specification fails to point to this as a particular embodiment of the claimed genus, and thus fails to describe this species. MPEP 2162 states, "Information which is well known in the art need not be described in detail in the specification". This is different from the instant situation, where the specification does not particularly teach that a modified version (isolated extracellular domain) of a particular prior art teaching (the full-length 75 kD sequence taught by Smith or Dembic) is a particular species of the claimed invention. Furthermore, the fact patterns of the cases cited by the Appellants and that of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections.

In *Capon v Eshhar*, as argued by Appellants, "both parties argued that their invention was the novel combination of DNA segments known in the art, not the discovery of the DNA segments themselves" (pages 21-22). The invention taught the particular regions to be fused (i.e., the variable region of an antibody" and "the transmembrane and cytoplasmic portions") and the rejection was based on a lack of a chimeric DNA sequence. This is different from the instant rejection where the specification does not describe a particular species of soluble fragment.

With respect to *Falkner*, Appellants argue (at pages 22-24) that in the Final Action (mailed 2/23/07), the Examiner erred in distinguishing the fact pattern of *Falkner* and the instant application. Appellants argue that Falkner disclosed general teachings with vaccine virus vectors, a specific example of poxvirus and working examples with a different virus (herpesvirus), and the instant specification is analogous in that it

discloses general teachings with TNF receptors, a specific example of the 75 kD TNF receptor, and a working example with the 55 kD TNF receptor. Appellants argue that the instant specification even provides more information than was provided by the Inglis '040 application in *Falkner*, because the instant specification provides the precise 75 kD TNF receptor sequence in Figure 4, discloses a reference (Smith, 1990) that contains the complete sequence, has a working example with a 55 kD TNF receptor that was not explicitly limited to 55 kD insoluble human TNF receptor, and describes TNF receptors and their use in particular for the presently claimed invention.

These arguments have been fully considered but are not found to be persuasive. It is maintained that the fact patterns of the case cited by the Appellants and of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections. As noted in *Falkner*, the disclosure of the Inglis '040 application does not have a description of poxvirus essential genes and relies on the fact that poxvirus essential genes were well-known in the art at the time of the effective filing date. The specification of the Inglis '040 application does have a detailed description and working examples with closely related herpes virus-based vaccines, teaches that the "invention can be applied to any virus where one or more essential gene(s) can be identified and deleted from or inactivated within the virus genome" and makes includes several references to poxvirus. So, the disclosure of the Inglis '040 application describes, in great detail, how to make a vaccine with one type of virus (herpes), which provides a description for the skilled artisan regarding how to make a vaccine with a second type of virus (poxvirus). This is distinguished from the instant case because (1) no members of the genus encompassed by "human TNF-binding soluble fragment" of a 75 kD insoluble receptor were "well-known in the art" (as set forth in the rejection); and (2) there is nothing disclosed in the instant specification that is analogous to the herpes virus-based vaccine of Inglis, upon which the skilled artisan could rely as guidance to extend the teachings of the specification to select a "human TNF-binding soluble fragment" of 75 kD insoluble receptor. Appellants argue that working examples in the specification with the 55 kD receptor provide the necessary guidance to provide a written description of a soluble fragment of the 75 kD. This

argument has been fully considered but is not found to be persuasive. While the specification on page 20 indicates that the specific examples are not intended to be limiting, there is no teaching in the specification that the teachings with respect to the 55 kD receptor can be applied to "TNF-binding proteins" in general. Furthermore, there is no description of how to select a "human TNF-binding soluble fragment" that can be applied to the genus of "TNF binding proteins" that include both the 55 kD and the 75 kD insoluble receptor. In the instant specification, Example 11 does indicate that "the extracellular region of the 55 kD TNF-BP" was used to construct an immunoglobulin fusion protein. However, there is no teaching that this "extracellular domain" is a TNF-binding fragment and there is no teaching in the specification indicating that a similar region should be used with the TNF-binding 75 kD insoluble receptor, or with TNF-binding insoluble receptors in general. Furthermore, the specification generally teaches away from using the entire extracellular domain of the 75 kD receptor as a species of soluble fragment. First, while the full-length 75 kD TNF receptor was known in the art, the application when discussing the invention repeatedly refers to a partial sequence encoded by SEQ ID NO: 4, and fragments thereof. On page 3, the "Summary of the Invention" states, "This invention also comprises TNF-binding proteins containing amino acid sequences of Figure 1 or Figure 4, proteins containing fragments of these sequences, and proteins analagous [sic] to the sequence of Figure 1 or Figure 4 or to fragments thereof" (page 3, lines 25-29). Thus, the specification points the skilled artisan to fragments of Figure 4 and not fragments of the full-length TNF-binding 75 kD insoluble receptor. On page 5 the "Detailed Description of the Invention" states that "[t]he TNF-binding proteins of the present invention include homogenous proteins containing the amino acid sequence depicted in Figure 1 or in Figure 4, proteins containing fragments of either sequence, and analogs of any such proteins for example proteins containing amino acid sequence analogous to the amino acid sequences of Figure 1 or Figure 4 or to fragments thereof. An analogue is a protein in which one or more amino acids of the sequence depicted in Figure 1 or in Figure 4 have had their side-groups chemically modified in a known manner, or those in which one or more amino acids have been replaced or deleted, without thereby eliminating TNF-binding

ability" (page 5, lines 11-24). The phrase "without thereby eliminating TNF-binding ability" implies that the sequence of Figure 4 has TNF-binding ability. However, Figure 4 depicts a partial amino acid sequence starting at residue 49 of the mature 75 kD TNF receptor as taught by Smith and Dembic, and thus missing a portion of critical residues 10-54 identified by Chan (2000). Thus, while the specification implies that SEQ ID NO: 4 has TNF-binding ability, the art shows that the sequence of Figure 4 does not have TNF-binding ability.

The only cDNA in the specification related to 75 kD receptor (SEQ ID NO: 3) is shown in Figure 4. Thus, even if the teachings of Example 11 were applied to the 75 kD receptor, it would only result in amplification of a cDNA encoding a protein with a partial extracellular domain of the 75 kD receptor, which as shown by the post-filing art (Chan, 2000) would not bind TNF. The specification does not contemplate use of the full-length extracellular domain of a 75 kD TNF-binding insoluble receptor, and in fact teaches away from this particular species as described above.

(c) Appellants' argument that the Examiner erred by substituting an unsupported interpretation of the specification for factual evidence (pg 24-29).

At page 24, Appellants argue that the Examiner erred "by substituting an unsupported personal interpretation of the specification for factual evidence in the Lyman Declaration regarding what the specification conveyed to the skilled artisan". Appellants argue that the "failure to provide evidence to support a factual assertion in the face of a challenge constitutes a clear and reversible error" and in support cite *In re Alton*, *Ex parte Natale*, and *In re Spormann*. At page 29, Appellants argue that "Appellants' declaration evidence must given consideration and due weight" and point to *Scripps Research Institute versus Genentech Inc* (2005).

These arguments have been fully considered but are not found to be persuasive. The Lyman Declaration (submitted 8/6/07; Page B-143 of the Appeal Brief) was fully considered and given due weight. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in

the outcome of the case, and the presence or absence of factual support for the expert's opinion. See *Ex parte Simpson*, 61 USPQ2d 1009 (BPAI 2001), *Cf. Redac Int'l. Ltd. v. Lotus Development Corp.*, 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), *Paragon Podiatry Lab., Inc. v. KLM Lab., Inc.*, 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). Furthermore, as stated in MPEP 716.01.III (citing *In re Chilowsky*, 306 F.2d 908,134 USPQ 515 (CCPA 1962)), expert opinion that an application meets the requirements of 35 U.S.C. 112 is not entitled to any weight; however, facts supporting a basis for deciding that the specification complies with 35 U.S.C. 112 are entitled to some weight. In the instant case, the preponderance of the evidence supports that the skilled artisan would not have held that in the instant specification that the full-length extracellular domain of the human TNF-binding 75 kD insoluble receptor is a particularly described species of the genus of "human TNF-binding soluble fragments" of the human TNF-binding 75 kD insoluble receptor.

In assessing the weight to be given expert testimony in the instant rejection, the examiner has considered the following. The nature of the fact to be established can be described as complex subject matter, in that it is directed novel biological molecules. The record does not establish any particular personal interest of the expert in the outcome of the case. Opposing evidence is present in the form of the teachings of the specification itself, as well as the teachings of Smith (1990), Dembic (1990) and Chan (2000). This evidence is summarized in the last two paragraphs of the preceding section of this Answer, which concluded that the specification does not contemplate use of the full-length extracellular domain of a 75 kD TNF-binding insoluble protein and in fact teaches away from this particular species. The presence or absence of factual support for the expert's opinion is discussed below.

The statements made at pages in paragraphs 1-7 and 11 of the Declaration are not disputed.

In paragraph 8, the Declaration states, "One of skill in the art as of September 10, 1990 would have understood that the application used the term "soluble fragment" to mean a fragment of the full length receptor missing the intracellular and transmembrane regions". Appellants point to page 3, lines 14-16 of the specification,

which states “Moreover, the TNF-binding proteins described in the state of the art are soluble, i.e., non-membrane bound, TNF-BP”. The Declaration states that, “[t]hus, the term “soluble fragment” refers to the extracellular domain of a TNF receptor or fragments of this domain”. Paragraph 8 further states, “one of skill in the art would have expected that the extracellular region of TNFR [TNF receptor] would bind to TNF”. In paragraph 9, the Declaration states that the use of the term soluble fragment in the application is consistent with how the term was used in the art at the time.

These statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. It is not disputed that the term “soluble fragments” can refer either to the extracellular domain of a TNF receptor or to fragments of this domain, or that this usage is consistent with how it was used in the art at the time of filing. However, the term broadly encompasses any “soluble fragment” of an insoluble receptor, and does not point in particular to a full-length extracellular. The instant specification provides only a partial sequence of the extracellular domain (SEQ ID NO: 4; which is missing residues critical for TNF binding as evidenced by Chan (2000; described above)), and guides the skilled artisan only to soluble fragments taken from this sequence (page 3, lines 25-29 and page 5, lines 11-24). Therefore, the instant specification provides evidence that the soluble fragments are only fragments of the partial extracellular domain of SEQ ID NO: 4. Therefore, reference to “soluble fragments” in the specification does not provide a written description of the regions of the full-length extracellular domain necessary to construct a soluble fragment with TNF-binding properties. The specification actually guides the skilled artisan to a collection of fragments that fail to have the required activity, and has no description of the structure of a binding fragment. Examiner does not dispute that the skilled artisan would have expected the full-length extracellular region of the 75 kD insoluble TNF receptor to bind to TNF. However, for the reasons set forth previously and maintained herein, the specification does not provide a description of the use of such full-length sequences in a soluble fragment, nor indicate that such sequences are even a part of the invention.

At page 25-26 of the Appeal Brief, Appellants point to paragraphs 10 and 12 of the Declaration and argue that the skilled artisan would have known that the application

contemplated the extracellular region of the TNF binding protein as a particular, specifically described example of a soluble fragment (page 10, lines 19-23 of the specification) and that the application further contemplated use of said fragment in an Ig fusion protein (Example 11 in the specification). In Paragraph 17, the Declaration points to page 20, lines 27-30 of the specification and states that any teachings made with regard to the 55 kD TNF receptor should apply equally to the 75 KD TNF receptor.

These arguments and the statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. Paragraphs 10, 12 and 17 set forth an opinion that the specification provides a written description of the full-length extracellular domain, but the only evidence in support of this opinion is the expert's interpretation of the specification. This has been fully considered, but the specification provides more evidence that it does not support a written description of the full-length extracellular domain. Page 10, lines 19-23 and Example 11 provide teachings that are directed solely to the 55 kD protein, and there are no corresponding teachings directed to the 75 kD protein. The teachings on page 10 that are directed to the 75/65 kD protein only refer to proteins that contain the partial sequence shown in Figure 4, and soluble fragments thereof. Nowhere does the specification provide the full-length extracellular sequence of the 75 kD protein, or indicate that this sequence is part of the invention. Page 20, lines 27-30 of the specification merely states that the invention has been described in general terms and that details that are provided are not intended to limit the invention. Such a statement is not sufficient to direct the skilled artisan to the particular invention that is now claimed. In *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed Cir. 2000), the court noted that with respect to *In re Ruschig* 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that “Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say “here is my invention”. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure”.

At pages 26-27 of the Appeal Brief, Appellants argue that the Examiner failed to address the factual evidence provided by the Lyman Declaration at paragraph 18-22

"showing why the Examiner's interpretation of the reference to Smith (1990) in the specification at page 10 was "illogical"". Appellants further argue that the Lyman Declaration states that the reference to Smith (1990) must be read in context of the entire application; that the Declaration states that the skilled artisan would not ignore a publicly available sequence to complete a partial cDNA sequence such as found in Figure 4; and that the skilled artisan would not have interpreted the reference to Smith to refer only to deletions of the sequence of Figure 4. In paragraphs 14-16 and 18-22, the Declaration states that Appellants knew of Smith (1990) when the application was drafted as evidenced by the citation therein. Paragraph 23 of the Declaration states that the skilled artisan would not have read the application without reference to any other known invention. The Declaration points to Dembic (1990) as also teaching the full-length sequence of the 75 kD receptor.

These arguments and the statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. Rather than providing "factual evidence", paragraphs 18-22 instead set forth an opinion that it is "illogical" that the reference to Smith (1990) on page 10 refers only to deletion from the sequence from Figure 4. The only evidence in support of this opinion is the expert's interpretation of the specification. This has been fully considered, but the specification itself provides more evidence that the reference to Smith (1990) does not support a written description of the full-length extracellular domain. The sentence referring to Smith is extremely specific (referring to "one sequence") and clearly states, “One sequence which results from such a deletion is described for example, in Science 248, 1019-1023 (1990)”. The immediate previous sentence in the specification refers to “deletions, substitutions and additions from one or more nucleotides of the sequence given in Figure 1 or 4.” There are no other references to Smith in the specification. There is no evidence in the specification of a description of using the sequences in Smith to complete the sequence of Figure 4, or even that the protein sequence of Figure 4 (SEQ ID NO: 4) needs to be completed for TNF binding (Chan (2000) as described above provides evidence that the missing residues from SEQ ID NO: 4 are critical for TNF binding). Thus, it is maintained that the preponderance of the evidence indicates that the reference to Smith is only in regard to

a deletion from the sequence found in Figure 4. While the skilled artisan might consider this teaching to be "illogical", because Smith does not clearly teach any such deletions from SEQ ID NO: 4, such an "illogical" teaching in the specification is only further evidence that the specification fails to provide a written description of the particular TNF-binding sequences that are important to the invention. There is no corresponding statement that the full-length extracellular domain disclosed by Smith is part of the instant invention, even when considered in the context of the entire paragraph or specification. The contention in paragraph 20 of the Lyman Declaration that the reference to Smith refers to "whatever soluble or non-soluble fragments of TNF binding proteins were described in the article" goes far beyond the teachings of the specification. There are no teachings in the full paragraph or the entire specification that direct the skilled artisan to what is required for functional TNF-binding soluble fragments. In *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed Cir. 2000), the court noted that with respect to *In re Ruschig* 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that "*Ruschig* makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure".

Furthermore, as described in the rejection set forth above, Smith only describes a putative region (residues 39-200, equivalent to 18-200 as taught by Dembic) in the extracellular domain that binds TNF, and does not actually teach any soluble or non-soluble fragments that bind to TNF and the post-filing art (Chan, 2000) provides evidence that a region (amino acids 10-54) containing other residues outside the region taught by Smith are critical for ligand-binding.

Furthermore, while a skilled artisan might use a publicly available sequence (such as taught by Smith or Dembic) to complete a partial sequence in SEQ ID NO: 4, this type of use also goes far beyond what is taught by the instant specification. Adequate written description requires more than a mere statement that a compound is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and

Amgen Inc. v. Chugai Pharmaceutical Co Ltd 18 USPQ2d 1016. In the instant case, there is not even a teaching of a potential method of isolating the full-length extracellular domain (e.g., by using Smith or Dembic to complete the partial sequence of SEQ ID NO: 4). In fact, there is not even a teaching that the full-length extracellular domain is important to Appellant's own invention. Therefore, the skilled artisan would not have viewed that Appellants had possession of an invention using the full-length extracellular domain at the time of filing of the application.

At pages 27-28, Appellants argue that the Lyman provides further "factual evidence in paragraphs 13-16 and 23 that the skilled artisan would look to the already-known sequences of Smith (1990) and Dembic [Appendix B-80] to find the complete p75 TNFR sequence". Appellants argue that the Examiner misinterpreted the teaching at page 14, lines 32-36 as referring to the sequences of Figure 1 and 4 rather than the "already known sequences" taught in the prior art.

These arguments and the statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. Rather than providing "factual evidence", paragraphs 13-16 and 23 instead set forth an opinion that the "already known sequences" mentioned on page 14 must refer to the sequences in Smith and Dembic, and that the skilled artisan would use these sequences to complete the partial 75 kD TNFR sequence shown in Figure 4. The only evidence in support of this opinion is the expert's interpretation of the specification. This has been fully considered, but the specification itself provides stronger evidence that the "already known sequences" refers to the sequence of Figure 1 and Figure 4. The sentence on page 14, lines 32-36 states that "On the basis of the thus determined sequence and of the already known sequences for certain receptors, those partial sequences which code for soluble TNF-BP fragments can be determined and cut out from the complete sequence using known methods [42]". The paragraph from which this sentence is taken describes using the sequences of "Figure 1 as well as Figure 4" to design oligonucleotides to probe cDNA or genome banks for related sequences (see page 42, lines 6-15 and lines 27-30). Thus, in context the phrase "thus determined sequence" refers to a hypothetical newly identified sequence from a cDNA or genome bank and

"already known sequences" refers to the sequences of Figure 1 or 4. Reference "[42]" in the quoted sentence is identified on page 46 as Sambrook (1989) which is a general text describing molecular cloning techniques, and which does not teach any "already known sequences" that bind TNF. Thus, there is no reference in the paragraph to any other "already known sequences" such as Smith (1990), and is nothing leading the skilled artisan from this paragraph back four pages to the single reference to the Smith (1990) on page 10, line 10 of the specification. Appellants further argue that the Lyman Declaration at paragraph 16 provides evidence that it would be clear to the skilled artisan that the protein sequence shown in Figure 4 is the same as the one described in Smith. While the Lyman Declaration provides evidence that at the time of filing one of skill in the art would look to publications in the prior art to complete the sequences of partial cDNAs, this evidence is not sufficient to overcome the rejection, because even if the skilled artisan recognized that Figure 4 is a partial sequence of the sequence taught in Smith, there is still nothing in the instant specification contemplating particular use of the full-length extracellular domain as a soluble fragment in the claimed protein. Adequate written description requires more than a mere statement that a compound is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical* Co Ltd 18 USPQ2d 1016.

In summary, the preponderance of the evidence supports that the skilled artisan would not have held that the instant specification describes the full-length extracellular domain of the human TNF-binding 75 kD insoluble receptor is a particularly described species of the genus of "human TNF-binding soluble fragments" of the human TNF-binding 75 kD insoluble receptor.

Finally, even if Appellants were in possession of a human TNF-binding soluble fragment comprising the full-length extracellular domain of the human TNF-binding 75 kD receptor, this would not provide written description of the genus of TNF-binding soluble fragments encompassed by the claims, for the reasons set forth in the rejection.

(d) Appellants' argument that the Examiner's interpretation of claim terms led to an erroneous conclusion that Appellants lacked adequate written description to support the breadth of the claims (pg 29-35).

At pages 29-35, Appellants set forth three sections of arguments (labeled (i) to (iii)) as to how the specification provides written description for the full scope of the claims. Each section is addressed in turn.

(i) Appellants' argument of erroneous claim interpretation (pg 30-32).

At pages 30-31, Appellants argue that the claims have been erroneously characterized as directed to a vast genus of soluble fragments ranging from the entire extracellular domain to a fragment as small as one amino acid that binds TNF, but that the interpretation that "human TNF-binding soluble fragments" include those with only one amino acid is unreasonable and factually unsupported. Appellants point to Smith (1990; page B-211 of the 2/28/08 Appeal Brief) as stating that the TNF-binding site is presumably contained within amino acids 1-162 of the mature 75 kD TNF receptor. Appellants point to U.S. Patent 5,395,760 (1995; page B-219 of the of the 2/28/08 Appeal Brief) as confirming the teachings of Smith by showing that fragments consisting of amino acids 1-235, 1-184 and 1-163 exhibited TNF-binding and further showing that a truncation to residues 1-142 destroys TNF binding activity. Appellants argue that "one would conclude that fragments shorter than 1-142, for example 5-142 or 10-142, will not bind TNF" and point to the requirement for amino acids 10-54 as taught by Chan (2000).

These arguments have been fully considered but are not found to be persuasive. Appellants mischaracterize the basis of the rejection. As stated on page 12 of the Final Action (mailed 2/23/07), "[t]he scope of the amended claims is such that the potential TNF-binding fragment of the receptor can comprise the entire extracellular domain or any fragment thereof as small as one amino acid that retains TNF-binding". The Examiner did not state, as argued by Appellants, that fragments as small as one acid would bind to human TNF. Instead, this statement described the potential scope of the claims in the absence of Appellants' description of the essential regions of the 75 kD receptor that are required for TNF-binding. The specification presents the skilled artisan

with a genus of "soluble fragments" derived from a human TNF-binding 75 kD insoluble receptor, and such a genus encompasses a fragment that is as small as one amino acid, and furthermore includes mutated variants of such. The specification further presents the skilled artisan with a functional characteristic of "human TNF-binding". What is missing is any correlation between the structure of the soluble fragments and functional ability to bind TNF.

Furthermore, the claims do not recite the minimal structure required for TNF binding. The binding site for TNF in the 75 kD receptor is not recited, nor is it disclosed in the specification. The claims do not recite the specific structural requirements essential for the required activity (TNF binding), but instead are intended to encompass any fragment of any size or location in the full-length protein that has the required activity (TNF binding).

Smith (1990) does not teach that residues 1-162 of the mature 75 kD TNFR presumably contain the binding site. Instead, Smith (1990) teaches that, "[t]he NH_2-terminal 162 amino acids (positions 39 to 200) are rich in cysteines (22 residues)..." (pages 1020-1021) and "[t]he net charge associated with the cysteine-rich domains of these family members varies ... which may be related to ligand specificity. Presumably, it is this NH_2-terminal region that contains the TNF binding site" (page 1021). Residues 39-200 taught by Smith include a signal sequence in their numbering and correspond to residues 18-179 of the mature protein (as taught by Dembic, 1990; page B-80 of the 2/28/08 Appeal Brief). However, this prior art teaching is only a hypothesis that residues 39 to 200 (18-179 according to Dembic) are crucial for the insoluble receptor to bind TNF; Smith does not actually provide any evidence that these residues are actually sufficient for TNF-binding or teach that soluble fragments consisting of these residues will bind to TNF. In fact, the post-filing art (Chan, 2000) provides evidence that a region (amino acids 10-54) containing other residues outside the region taught by Smith are critical for ligand-binding. Therefore, the evidence does not support Appellants' position.

Appellants point to U.S. Patent No. 5,395,760 as confirming that truncations (such as a fragment of residues 1-142) destroy TNF-binding activity. However, this patent was published in 1995 and does not provide any teachings that inform the

teachings of the instant specification at the time of the effective filing date. Instead, the '760 patent provides evidence supporting the lack of correspondence between the structure (any soluble fragment) and function (human TNF-binding) in the claims at the time of the effective filing date. The instant specification does not describe which particular fragments will be able to bind TNF (such as the fragments consisting of residues 1-235, 1-184 or 1-163 taught by the '760 patent) and which will not bind TNF (such as the fragment consisting of residues 1-142 taught by the '760 patent). The '760 patent provides evidence of the further act of invention which was required to provide adequate written description for the TNF-binding soluble fragments recited in the instant claims but not described in the instant specification.

At page 31, Appellants argue that the interpretation of the term "human" in the phrase "human TNF receptor" as including variants with any number of mutations has no basis in the specification or the art, and is not supported by the evidence. Appellants argue that the broadest reasonable interpretation of the claims must be consistent with the specification (citing *In re Buszard* (2007) and *Merck v. Teva* (2003)), and that there is no definition of "human" in the specification and therefore it is wrong to conclude that "human" includes artificial receptors with one or more mutations. Appellants argue that they have stated on the record that the term "human" refers to naturally-occurring 75 kilodalton (kD) human TNF receptor and this definition is consistent with the art. Appellants point to Figure 3 of Smith (1990) as teaching the sequence of the "human TNF receptor cDNA clone" obtained from a "human cDNA library" and to Dembic (1990) as being titled "Two Human TNF Receptors" and teaching that the 75 kD TNF receptor clone was obtained from a human library.

These arguments have been fully considered but are not found to be persuasive. This interpretation of the claim is not an unsupported personal interpretation; rather, the preponderance of the evidence supports that the skilled artisan would have held the term "human TNF receptor" to encompass variants with any number of mutations. The specification clearly states that the invention "embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4, whereby in the case

of the proteins coded thereby there come into consideration, just as before TNF-BP" (page 10,lines 1-9) and "is also concerned with DNA sequences which comprise a combination of two partial sequences, with one of the partial sequences coding for those soluble fragments of non-soluble portions which bind TNF (see above) and the other partial sequences coding for all domains other than the first domain of the constant region of the heavy chain of human immunoglobulins such as IgG, IgA, IgM or IgE, in particular IgG1 or IgG3 subtypes" (page 11, lines 1-10). These teachings provide evidence that the specification particularly contemplates fusion proteins encompassing variants with one or more mutations in the TNF-binding soluble fragment. Furthermore, the specification uses the term "human" to refer to other artificially-modified versions of naturally-occurring human products. Specifically, cell lines that are artificially isolated and growing apart from the human body are referred to as "human cell lines" (page 16, line 36) and human TNF that is artificially modified by radioiodination is referred to as "human radioiodinated 125I-TNF" (page 20, lines 35-36). As the specification does not contain a limiting definition of the term "human TNF receptor", the broadest reasonable interpretation consistent with the above teachings of the specification is that the term "human TNF receptor" includes a human TNF receptor with one or more mutations. The use of the term "human" in the references of Smith and Dembic does is merely exemplary and is not limiting; Smith and Dembic provide examples of a naturally-occurring human sequence and do not comment on whether mutated versions would also be labeled "human". Therefore, Smith and Dembic are not considered to provide evidence of a limiting definition of the term "human" as used with respect to the 75 kD human TNF receptor.

At page 32, Appellants further argue that the physical characteristics of the human TNF receptor, including binding to human TNF, having a molecular weight of about 75 kD, and comprising the sequence of SEQ ID NO: 10 render it uniquely identifiable. Appellants point to evidence previously submitted that shows that a June 14, 2006 search using SEQ ID NO: 10 in a "comprehensive national databases of all publicly available "human" amino acid sequences" only identifies the human 75 kD insoluble TNF receptor sequence or naturally occurring allelic variants thereof.

These arguments have been fully considered but are not found to be persuasive. Appellants' results from searching human sequence databases in 2006 are not disputed. However, even if the physical characteristics of a 75 kD insoluble human TNF receptor render it "uniquely identifiable", the claims are not limited to this sequence. The specification specifically contemplates analogues of the sequence of Figure 4 with one or more amino acid replacements or deletions but that retain TNF-binding (page 5, lines 17-23) and that these analogues may be modified by genetic engineering (page 7, line 4). One or more replaced (i.e., substituted) amino acids would not substantially change the molecular weight of the 75 kD protein; it would remain "about 75 kD" as recited in the claims. Thus, the "insoluble receptor" of the claims encompasses not only the "uniquely identifiable" natural sequence as argued by Appellants, but also mutated variants in which one or more amino acids are changed (with no limit) and that retain the ability to bind human TNF, a molecular weight of about 75 kD, and the SEQ ID NO: 10 (which is only 18 amino acids in length). The claims encompass soluble fragments of these receptors that retain TNF-binding, and thus the soluble fragments also include one or mutations to a naturally-occurring human sequence.

(ii) Appellants' argument of a representative number of species (pg 32-34).

At pages 32-34, Appellants argue that the specification satisfies the written description of the claimed genus through sufficient description of a representative number of species. Appellants argue that the specification contemplates a variety of TNF-binding soluble fragments of TNFR and teaches assays to determine TNF-binding. Appellants further argue that the claimed genus does not include truncations to amino acids 1-142 or smaller because the art (U.S. Patent 5,395,760, published in 1995) shows that fragments this small will not bind TNF. Appellants argue that the claimed genus is limited to fragments that are between 162 and 235 residues in length (the full-length of the extracellular domain is 235 residues), and that three representative species are provided by Smith (1990) and of Dembic (1990); Appellants provide a figure showing these species on page 34 of the 2/28/08 Appeal Brief.

These arguments have been fully considered but are not found to be persuasive. It is not disputed that the written description of a claimed genus can be satisfied through sufficient description of a representative number of species. However, in the instant case the specification does not provide sufficient description of a representative number of species of a human TNF-binding soluble fragment of a TNF-binding 75 kD insoluble human receptor.

With respect to the use of assays to determine whether soluble fragments can bind TNF, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co.* Ltd., 18 USPQ2d 1016. In *University of Rochester v. G.D. Searle & Co.*, 358 F. 3d 916 (Fed. Cir. 2004) the court held that a description of screening assays that could be used to identify compounds that have a particular characteristic was not sufficient to describe said compounds.

With respect to the U.S. Patent No. 5,395,760, this patent was published after the effective filing date for the claimed protein and does not provide any teachings that inform the teachings of the instant specification at the time of the effective filing date. The specification as filed does not provide a description that fragments of residues 1-142 will not bind TNF. Instead, the specification presents the skilled artisan with a genus of "soluble fragments" and a functional limitation of "TNF binding" and does not describe which fragments will bind, and does not describe which particular fragments will be able to bind TNF (such as the fragments consisting of residues 1-235, 1-184 or 1-163 taught by the '760 patent) and which will not (such as the fragment consisting of residues 1-142 taught by the '760 patent). In fact, the specification particularly points to fragments of the sequence of Figure 4 (SEQ ID NO: 4) which would not have had the required TNF binding activity, as evidenced by the post-filing date publication of Chan (2000).

With respect to the teachings of Smith (1990) and Dembic (1990), these publications do not provide teachings of any species of human TNF binding soluble fragments that were well known in the art. The earlier reference is Smith (1990), who teaches only that, "[t]he NH_2-terminal 162 amino acids (positions 39 to 200) are rich in

cysteines (22 residues)..." (pages 1020-1021) and "[t]he net charge associated with the cysteine-rich domains of these family members varies ... which may be related to ligand specificity. Presumably, it is this NH_2-terminal region that contains the TNF binding site" (page 1021). Residues 39-200 taught by Smith include the leader signal sequence in their numbering and correspond to residues 18-179 as taught by Dembic. [Appellants repeatedly refer to this region identified by Smith incorrectly as amino acids 1-162 rather than amino acids 39-200]. Importantly, Smith only teaches this species as a hypothetical binding region in the extracellular domain of the insoluble receptor. Smith does not teach this region can be isolated as a soluble fragment that will bind to TNF. In fact, the post-filing art (Chan, 2000) provides evidence that a region (residues 10-54) including residues outside of this region is critical for ligand-binding.

The naturally-occurring soluble TNF-binding protein that exists in human serum taught by Dembic is not fully characterized. It has an NH_2-terminal sequence that matches a sequence starting with the fifth amino acid of the full-length 75 kD insoluble receptor, but while Dembic further teaches that this soluble protein is "presumably of the extracellular region" of the receptor (page 235), Dembic does not teach the size of this soluble protein or indicate how much of the extracellular region it comprises (as indicated by the question marks by this species in the figure on page 34 of the Appeal Brief). Thus, the sequence of this soluble protein cannot be considered to be "well-known" in the art and cannot be a species of "soluble fragment" described by the instant application in the absence of any explicit description thereof. Dembic also teaches a "schematic representation" of the 235-amino acid extracellular region of the 75 kD insoluble receptor that shows four domains of cysteine rich repeats (Figure 2 on page 233). However, Dembic does not teach which residues in the extracellular region are required for TNF-binding. Dembic further does not teach the full-length extracellular domain as a soluble fragment that will bind to human TNF.

Thus, while Dembic and Smith generally teach that the TNF-binding region of the insoluble receptor is found in particular regions of the extracellular domain, they do not teach the sequence of any species of soluble fragment that can bind to human TNF. Furthermore, Dembic and Smith do not particularly point to the full-length extracellular

domain as a soluble fragment of the 75 kD receptor. Thus, the instant specification cannot rely on the teachings of these publications as providing species of "soluble fragments" that were well-known in the art. Furthermore, as described above, the specification generally teaches away from the using the full-length extracellular domain by repeatedly referring to fragments of the sequence of Figure 4, for which the post-filing art provides evidence will not bind TNF. Thus, it is maintained that the specification teaches that the invention is concerned with TNF-binding soluble fragments but fails to provide a single species in support of this vast genus.

(iii) Appellants' argument that the specification provided functional and structural characteristics and a known correlation between them (pg 34-35).

At pages 34-35, Appellants argue that a genus may be adequately described by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics (citing *Enzo Biochem, Inc. v. Gen-Probe Inc* (2002) and *Amgen Inc v Hoechst Marion Roussel, Inc* (2003). Appellants argue that adequate written description based on the recited function (TNF binding), the physical identifying characteristics of 75 kD insoluble TNF receptor, and the known correlation between said recited function and structure. Appellants point to an assay for TNF binding taught in Example 1 of the specification. Appellants argue that common structural features of the claimed genus were known in the art at the time of filing such as the teachings of Smith (1990) including the extracellular domain (residues 1-235) and the "likely TNF binding site" (residues 1-162) and that the skilled artisan would have expected the full-length extracellular region to bind TNF. Appellants argue that the recited characteristics of the insoluble TNF receptor (including that it is human, has a molecular weight of about 75 kD, and comprises the peptide of SEQ ID NO: 10) provide adequate structural definition for the claimed TNF-binding soluble fragment. Appellants further argue that factual evidence was submitted Appendix B-195) showing that SEQ ID NO: 10 is sufficient to uniquely identify the 75 kD insoluble human TNF receptor. Appellants argue that the Examiner's failure to comment

on this evidence in the Final Action was legal error because patentability requires consideration of the totality of the record including all arguments and evidence.

These arguments have been fully considered but are not found to be persuasive. It is not disputed that a genus may be adequately described by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics. However, in the instant case the correlation between the structure of the naturally-occurring human 75 kD TNF insoluble receptor and its function (TNF binding) does not equate with a correlation between the structure of a genus of human TNF binding soluble fragments as recited in the claim, including fragments of both the naturally-occurring receptor as well as mutated variants therefore. The post-filing date art teaches that the sequences of IID (SEQ ID NO: 10), IIB (SEQ ID NO: 8) and IIF (SEQ ID NO: 12) recited in the claims are not sufficient for TNF binding. In particular, U.S. Patent 5,395,760 (1995; page B-219 of the of the 2/28/08 Appeal Brief) shows that a truncation to residues 1-142 destroys TNF binding activity, and thus smaller fragments such as IID, IIB and IIF also could not bind TNF. Even the combination of all of these sequences would not be sufficient to provide TNF binding. Therefore, the recitation of these sequences in one or more of the claims does not provide sufficient structure to provide TNF binding for either the insoluble receptor or soluble fragments thereof. Even the narrowest of soluble fragments recited in part (a) of claim 128 only requires a total of 25 specific residues, (17 from SEQ ID NO: 10, 4 from SEQ ID NO: 12, 4 from SEQ ID NO: 8) of the extracellular domain of receptor (out of 235 amino acids). Thus, the claims still encompass variants in one or more of 235 positions in the extracellular domain, and the specification does not teach the sequences required for TNF binding.

Smith (1990) only teaches that, "[t]he NH_2-terminal 162 amino acids (positions 39 to 200) are rich in cysteines (22 residues)..." (pages 1020-1021) and "[t]he net charge associated with the cysteine-rich domains of these family members varies ... which may be related to ligand specificity. Presumably, it is this NH_2-terminal region that contains the TNF binding site" (page 1021). Residues 39-200 taught by Smith include the leader signal sequence in their numbering and correspond to residues 18-179 as taught by

Dembic. [Appellants repeatedly refer to this region identified by Smith incorrectly as amino acids 1-162 rather than amino acids 39-200]. Importantly, Smith only teaches this species as a hypothetical binding region in the extracellular domain of the insoluble receptor. Smith does not teach this region can be isolated as a soluble fragment that will bind to TNF. In fact, the post-filing art (Chan, 2000) provides evidence that a region (residues 10-54) including residues outside of this region is critical for ligand-binding.

With respect to the use of assays to determine whether soluble fragments can bind TNF, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co.* Ltd., 18 USPQ2d 1016. In *University of Rochester v. G.D. Searle & Co.*, 358 F. 3d 916 (Fed. Cir. 2004) the court held that a description of screening assays that could be used to identify compounds that have a particular characteristic was not sufficient to describe said compounds.

The evidence found in Appendix B-195 was fully considered in the 2/23/07 Final Action, and was commented on therein by the statements therein (at pages 11-12) that even if the specification provided a written description of fusion proteins comprising the full-length extracellular domain as known in the art (such taught by Smith or Dembic), the specification as filed does not provide a written description of the vast genus of protein variants encompassed by the claims. Appellants' results from searching human sequence databases in 2006 are not in dispute. The sequence taught by Smith or Dembic is the human sequence that would have been "uniquely identified" by a search in a database at the effective filing date. However, even if the physical characteristics of a 75 kD insoluble human TNF receptor render it "uniquely identifiable", the claims are not limited to this sequence. The specification specifically contemplates analogues of the sequence of Figure 4 with one or more amino acid replacements or deletions but that retain TNF-binding (page 5, lines 17-23) and that these analogues may be modified by genetic engineering (page 7, line 4). One or more replaced (i.e., substituted) amino acids would not substantially change the molecular weight of the 75 kD protein; it would remain "about 75 kD" as recited in the claims. Thus, the "insoluble receptor" of the

claims encompasses not only the "uniquely identifiable" natural sequence as argued by Appellants, but also mutated variants in which one or more amino acids are changed (with no limit) and that retain the ability to bind human TNF, a molecular weight of about 75 kD, and the SEQ ID NO: 10 (which is only 18 amino acids in length). The claims further encompass soluble fragments of these receptors that retain TNF-binding, and thus the soluble fragments also include one or mutations to a naturally-occurring human sequence. Thus, the structural features recited in the claims do not provide adequate structural definition for the claimed TNF-binding soluble fragment, because they only identify the naturally-occurring 75 kD insoluble receptor, and no other species of the vast genus of variants encompassed by the claims.

2. The written description rejection of claims 106, 125, 126 and 128 (pg 35-36).

In this section, Appellants advance the same four arguments as in section VII.A.1. Appellants additionally argue that claims 106, 125, 126 and 128 "recite additional peptide sequences with the human 75 kD TNF receptor sequence, namely SEQ ID NOs: 8, 9, 12 and 13". Appellants argue that while SEQ ID NO: 10 alone would have been sufficient to uniquely identify the human 75 kD TNF receptor sequence, that these additional sequences make unique identification certain.

These arguments have been fully considered but are not found to be persuasive. The four arguments repeated from section VII.A.1 have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 105, 107, 110, 111, 113, 114, 119, 120, 123, 124, 129, 130, 132, 133 and 137.

With respect to the additional peptide sequences recited in the claims, as noted in the rejection, the recited sequences represent the following sequences in the 75 kD insoluble TNF receptor taught by Dembic: 1-7 and 9-18 (IID, SEQ ID NO: 10); 43-47 (IIB, SEQ ID NO: 8); 66-69 (IIF, SEQ ID NO: 12) and 278-284 (IIG, SEQ ID NO: 13); 324-339 (IIC, SEQ ID NO: 9). It is not disputed that SEQ ID NO: 10, either alone or in combination with SEQ ID NO: 8, 9, 12 and 13, could "uniquely identify" a 75 kD TNF receptor sequence in a database. However, even if the physical characteristics of a 75

kD insoluble human TNF receptor render it "uniquely identifiable", the claims are not limited to this sequence. As described in detail in the rejection, the "insoluble receptor" of the claims encompasses not only the "uniquely identifiable" natural sequence as argued by Appellants, but also mutated variants in which one or more amino acids are changed (with no limit) and that retain the ability to bind human TNF, a molecular weight of about 75 kD, and the SEQ ID NO: 10 (which is only 18 amino acids in length). The claims further encompass soluble fragments of these receptors that retain TNF-binding, and thus the soluble fragments also include one or mutations to a naturally-occurring human sequence. Thus, the structural features recited in the claims do not provide adequate structural definition for the claimed TNF-binding soluble fragment, because they only identify the naturally-occurring 75 kD insoluble receptor, and no other species of the vast genus of variants encompassed by the claims.

Claims 106, 125, 126 and 128 also recite that the soluble fragments include SEQ ID NO: 8, 12 and/or 10. While the specification teaches these soluble fragments, it does not teach whether or not any of them can bind to TNF. However, the post-filing date art teaches that the "soluble fragments" of IID, IIB and IIF would also not bind TNF. In particular, U.S. Patent 5,395,760 (1995; page B-219 of the of the 2/28/08 Appeal Brief) shows that a truncation to residues 1-142 destroys TNF binding activity, and thus smaller fragments such as IID, IIB and IIF also could not bind TNF. Even the combination of all of these sequences would not be sufficient to provide TNF binding. Therefore, the recitation of these sequences in one or more of the claims does not provide sufficient structure to provide TNF binding for either the insoluble receptor or soluble fragments thereof. Even the narrowest of soluble fragments recited in part (a) of claim 128 only requires a total of 25 specific residues, (17 from SEQ ID NO: 10, 4 from SEQ ID NO: 12, 4 from SEQ ID NO: 8) of the extracellular domain of receptor (out of 235 amino acids). Thus, the claims still encompass variants in one or more of 235 positions in the extracellular domain, and the specification does not teach the sequences required for TNF binding.

3. The written description rejection of claims 121, 131, 134 and 136 (pg 36).

In this section, Appellants advance the same four arguments as in section VII.A.1. Appellants further argue that these claims recite "consisting of" and are therefore narrower than claims reciting "comprising". Appellants further argue that the fusion protein of these claims is specifically illustrated by the working example in the specification (Example 11) with the 55 kD insoluble receptor (here called "p55 TNFR").

These arguments have been fully considered but are not found to be persuasive. The four arguments repeated from section VII.A.1 have been fully considered, but are maintained for the same reasons set forth above for 62, 102, 103, 105, 107, 110, 111, 113, 114, 119, 120, 123, 124, 129, 130, 132, 133 and 137.

With respect to the recitation of "consisting of" in the claims, this argument has been fully considered but is not found to be persuasive because this recitation is outside of part (a) of claims 121, 131, 134 and 136. Thus, part (a) of claim 121 is identical to part (a) of parent claim 62; part (a) of claim 131 is identical in scope to part (a) of parent claim 107. Independent claim 134 and dependent claim 136 have the same scope as claim 102 with respect to part (a) of the protein. The use of "consisting" versus "comprising" in these claims only concerns the overall protein of the claim: whether the claimed fusion protein can contain additional sequences beyond the recited parts (a) and (b) (i.e., the protein comprises (a) and (b) and unrecited material) or whether the claimed fusion protein is limited to consisting of parts (a) and (b).

With respect to Example 11 in the specification, this argument has been fully considered but is not persuasive. Example 11 of the specification does not "specifically illustrate" the protein of claims 121, 131, 134 or 136. While the specification on page 20 indicates that the specific examples are not intended to be limiting, there is no teaching in the specification that the teachings with respect to the 55 kD receptor can be applied to "TNF-binding proteins" in general. Furthermore, there is no description of how to select a "human TNF-binding soluble fragment" that can be applied to the genus of "TNF binding proteins" that include both the 55 kD and the 75 kD insoluble receptor. In the instant specification, Example 11 does indicate that "the extracellular region of the 55 kD TNF-BP" was used to construct an immunoglobulin fusion protein. However, there is no teaching that this "extracellular domain" is a TNF-binding fragment and there

is no teaching in the specification indicating that a similar region should be used with the TNF-binding 75 kD insoluble receptor, or with TNF-binding insoluble receptors in general. Furthermore, the specification generally teaches away from using the entire extracellular domain of the 75 kD receptor as a species of soluble fragment. First, while the full-length 75 kD TNF receptor was known in the art, the application when discussing the invention repeatedly refers to a partial sequence encoded by SEQ ID NO: 4, and fragments thereof. On page 3, the "Summary of the Invention" states, "This invention also comprises TNF-binding proteins containing amino acid sequences of Figure 1 or Figure 4, proteins containing fragments of these sequences, and proteins analagous [sic] to the sequence of Figure 1 or Figure 4 or to fragments thereof" (page 3, lines 25-29). Thus, the specification points the skilled artisan to fragments of Figure 4 and not fragments of the full-length TNF-binding 75 kD insoluble receptor. On page 5 the "Detailed Description of the Invention" states that "[t]he TNF-binding proteins of the present invention include homogenous proteins containing the amino acid sequence depicted in Figure 1 or in Figure 4, proteins containing fragments of either sequence, and analogs of any such proteins for example proteins containing amino acid sequence analogous to the amino acid sequences of Figure 1 or Figure 4 or to fragments thereof. An analogue is a protein in which one or more amino acids of the sequence depicted in Figure 1 or in Figure 4 have had their side-groups chemically modified in a known manner, or those in which one or more amino acids have been replaced or deleted, without thereby eliminating TNF-binding ability" (page 5, lines 11-24). The phrase "without thereby eliminating TNF-binding ability" implies that the sequence of Figure 4 has TNF-binding ability. However, Figure 4 depicts a partial amino acid sequence starting at residue 49 of the mature 75 kD TNF receptor as taught by Smith and Dembic, and thus missing a portion of critical residues 10-54 identified by Chan (2000). Thus, while the specification implies that SEQ ID NO: 4 has TNF-binding ability, the art shows that the sequence of Figure 4 does not have TNF-binding ability.

The only cDNA in the specification related to 75 kD receptor (SEQ ID NO: 3) is shown in Figure 4. Thus, even if the teachings of Example 11 were applied to the 75 kD receptor, it would only result in amplification of a cDNA encoding a protein with a partial

extracellular domain of the 75 kD receptor, which as shown by the post-filing art (Chan, 2000) would not bind TNF. The specification does not contemplate use of the full-length extracellular domain of a 75 kD TNF-binding insoluble receptor, and in fact teaches away from this particular species as described above.

4. The written description rejection of claim 127 (pg 37-38).

In this section, Appellants advance the same four arguments as in section VII.A.1. Appellants further argue that these claims recite "consisting of" and are therefore narrower than claims reciting "comprising". Appellants further argue that the fusion protein of these claims is specifically illustrated by the working example in the specification (Example 11) with the 55 kD insoluble receptor (here called "p55 TNFR"). Appellants further argue that claim 127 recites additional peptide sequences found in the 75 kD TNF receptor as with parent claim 106. Appellants argue that while SEQ ID NO: 10 alone would have been sufficient to uniquely identify the human 75 kD TNF receptor sequence, that these additional sequences make unique identification certain.

These arguments have been fully considered but are not found to be persuasive.

The four arguments repeated from section VII.A.1 have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 105, 107, 110, 111, 113, 114, 119, 120, 123, 124, 129, 130, 132, 133 and 137.

With respect to the recitation of "consisting of" in the claims, this argument has been fully considered but is not found to be persuasive because this recitation is outside of part (a) of claim 127. Thus, part (a) of claim 127 is identical to part (a) of parent claim 106. The use of "consisting" versus "comprising" in this claim only concerns the overall protein of the claim: whether the claimed fusion protein can contain additional sequences beyond the recited parts (a) and (b) (i.e., the protein comprises (a) and (b) and unrecited material) or whether the claimed fusion protein is limited to consisting of parts (a) and (b).

With respect to Example 11 in the specification, this argument has been fully considered but is not persuasive for the same reasons for claim 121 above.

With respect to the "additional sequences" recited in claim 127, this argument has been fully considered but is not persuasive for the same reasons as for claim 106 above. The "additional sequences" recited in claim 127 are identical to those found in parent claim 106.

5. The written description rejection of claim 135 (pg 38).

In this section, Appellants advance the same four arguments as in section VII.A.1. Appellants further argue that these claims recite "consisting of" and are therefore narrower than claims reciting "comprising". Appellants further argue that the fusion protein of these claims is specifically illustrated by the working example in the specification (Example 11) with the 55 kD insoluble receptor (here called "p55 TNFR"). Appellants further argue that claim 135 recites additional peptide sequences found in the 75 kD TNF receptor. Appellants argue that while SEQ ID NO: 10 alone would have been sufficient to uniquely identify the human 75 kD TNF receptor sequence, that these additional sequences make unique identification certain.

These arguments have been fully considered but are not found to be persuasive.

The four arguments repeated from section VII.A.1 have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 105, 107, 110, 111, 113, 114, 119, 120, 123, 124, 129, 130, 132, 133 and 137.

With respect to the recitation of "consisting of" in the claims, this argument has been fully considered but is not found to be persuasive because this recitation is outside of part (a) of claim 134. Claim 135 does not even recite "consisting of" directly, but depends from claim 134 which recites "consisting of". Claim 135 depends from claim 134 and limits the soluble fragment to one that comprises SEQ ID NO: 10. Thus, claim 135 limits the soluble fragment of part (a), but the use of "consisting" versus "comprising" in this claim only concerns the overall protein of the claim: whether the claimed fusion protein can contain additional sequences beyond the recited parts (a) and (b) (i.e., the protein comprises (a) and (b) and unrecited material) or whether the claimed fusion protein is limited to consisting of parts (a) and (b).

With respect to Example 11 in the specification, this argument has been fully considered but is not persuasive for the same reasons for claim 134 above.

With respect to the "additional sequences" recited in claim 134, this argument has been fully considered but is not persuasive for the same reasons as for claim 128 above. The "additional sequences" recited in the soluble fragment of claim 134 are identical to those found in the soluble fragment of claim 128.

B. The obviousness rejection of claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121, 125-131 and 134-137 under 35 U.S.C. § 103 over Dembic et al (Cytokine 2: 231-237, 1990) in view of Capon (US Patent No. 5,116,964).

In this section of the Appeal Brief filed on 2/28/08, Appellants provide a "Brief Statement of Relevant Prosecution History" (pages 39-41) and then advance arguments why the rejection should be reversed (page 41-62). Appellants' statements regarding the prosecution history have been fully considered. No particular statements are disputed, but a response to the statement that, "[t]he Examiner did not explain why affinity purification compositions, which are not intended for administration to humans, would require sterile isotonic formulations" (page 40) is provided below in the section addressing the arguments against the rejection of the claims reciting "pharmaceutical compositions" (claims 114 and 137).

Appellants divide the arguments into eight sections by claim number. These arguments are addressed in the order presented in the Appeal Brief.

1. The obviousness rejection of claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (pg 41-55).

Appellants divide the arguments in this section into five parts (labeled "a" through "e"). These arguments are addressed in the order presented in the Appeal Brief.

a. Appellants' argument that the cited art teaches away from combining Capon with Dembic (pg 41-43).

Appellants argue that the teachings of *Capon* are primarily directed to providing molecules for *in vivo* administration. Appellants argue that soluble fragments of the 75 kD TNF receptor would be expected to have anti-inflammatory activity if administered, and that Capon teaches that the immunoglobulin heavy chain constant region has pro-inflammatory activity that is retained by fusion proteins of such, and thus the skilled artisan would have been discouraged from combining the two elements for *in vivo* administration. Appellants further argue that the motivation to combine the elements based on affinity purification (as asserted in the rejection) "is not rational because affinity purification of TNF was already easily carried out with anti-TNF antibody" (page 42). Appellants argue (citing *KSR*) that obviousness rejections "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness".

These arguments have been fully considered but are not found to be persuasive. As stated in MPEP 2123, “Patents are relevant as prior art for all that they contain” and “[t]he use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain” and “[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments.” The Examiner does not dispute that Capon teaches that the immunoglobulin heavy chain constant region has pro-inflammatory activity that is retained by fusion proteins of such, or that soluble fragments of TNFR could act as an anti-inflammatory agent. However, as set forth in the rejection, Capon also teaches that the hybrid immunoglobulins can be used for affinity purification of ligands (column 22, lines 5-6). This is a purely *in vitro* use for which an *in vivo* anti-inflammatory activity of the heavy chain constant region is not relevant. Furthermore, the ability to use antibodies to purify TNF does not negate the teachings of Capon regarding the use of binding agents fused to immunoglobulin heavy chain domains for ligand purification. The teachings of Capon present an alternative method of purification that adds to the existing knowledge base of the skilled artisan, rather than replacing it. As stated in MPEP 2123, "Disclosed examples and preferred embodiments do not

constitute a teaching away from a broader disclosure or nonpreferred embodiments". Therefore, Appellants' arguments regarding the "rationality" of modifying Capon in view of Dembic are not found to be persuasive.

b. Appellants' argument that there was no motivation to select the claimed fusion proteins which are homodimeric (pg 43-44).

At pages 43-44, Appellants argue that there was no motivation to select the particular species of claimed fusion proteins (which are homodimeric) from the large genus of fusion proteins disclosed in Capon, including the large subgenus of homodimeric fusion proteins. Appellants argue that "[t]he selection of a species from a large genus disclosed in the prior art is nonobvious" and point to *In re Baird* (1994). Appellants argue that the skilled artisan would have expected a "monomeric form lacking disulfide bonding, such as TNFR-CH_2CH_3 fusion, to bind TNF with greater certainty of success" (page 44). Appellants argue that Capon teaches homodimeric fusion proteins in which the CH1 domain and a portion of the hinge region is deleted (in Example 5) and that contain the entire heavy chain constant region, whereas the claims are directed to a different species of fusion proteins that contains all of the domains of the constant region of an IgG heavy chain other than CH1.

These arguments have been fully considered but are not found to be persuasive. The instant specification does not provide a definition of the term "all of the domains of the constant region of an IgG heavy chain other than CH1". The specification does not teach whether the term "domains" includes the "hinge" as well as the CH1, CH2 or CH3 domains. Thus, the recitation of "all of the domains of the constant region of an IgG heavy chain other than CH1" broadly encompasses sequences that just contain the CH2 and CH3 domains. Furthermore, this recitation does not exclude domains that are present in a partial or mutated sequence. Thus, the claims broadly encompass fusion proteins in which all, none or a portion of the "hinge" is present. Capon specifically teaches, "Typically, such fusions retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain" (column 10, lines 10, 12). This shows that preferred embodiments informing the genus taught by Capon

include those including each domain (CH2, CH3) of the constant region other than the first domain (CH1). With regard to the ability of a homodimeric species to bind TNF, Appellants refer to arguments in section "c"; therefore, these arguments are addressed in detail below. However, in summary it is maintained that the skilled artisan would have had a reasonable expectation that a homodimeric fusion protein would bind TNF. Thus, it is maintained that the skilled artisan would have been motivated to select a homodimeric species from among the genus taught by Capon.

c. Appellants' argument that the assertion of reasonable expectation of success was based on uncorroborated factual assumption (pg 44-46).

At pages 44-46, Appellants argue that the assertion of reasonable expectation of success set forth in the rejection was based on an "uncorroborated factual assumption" that the claimed dimeric fusion proteins would bind trimeric TNF. Appellants argue that the Lesslauer Declaration A (page B-129 of the Appeal Brief) describes that there was uncertainty that the spatial configuration of the dimeric TNF receptor fusion protein would allow it to bind a trimeric TNF ligand. Appellants point to the statement at page 2 of the Declaration that "the spatial geometry of the receptor binding site was unknown. Thus, it could have been possible that the fusion with IgG fragments created a spatial structure that would have contained TNF receptor sequence but which, due to its spatial structure, was completely unable to bind TNFα". Appellants further dispute that Smith and Baglioni (1989; cited previously) provide evidence that the TNF trimer was known at the time of filing to bind a complex of two 75 kD receptor molecules. Appellants argue that none of sequences in Smith and Baglioni have been shown to contain the particular sequences recited in the pending claims.

These arguments have been fully considered but are not found to be persuasive. It is conceded, as pointed out by Appellants, that Smith and Baglioni (1989) do not clarify specific receptor subunits found in the multimeric complexes, particularly in view of the later findings that two distinct receptor sequences exist (i.e., the 55 kD and 75 kD TNFRs). It is therefore conceded that this argument successfully weakens Smith and

Baglioni as evidence in support of a reasonable expectation of success. However, the rejection is maintained for the following reasons.

First, *KSR Int'l. Co. v. Teleflex Inc.* (2007) states "if a person of ordinary skill artisan can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill" reasonable expectation of success. Thus, in view of *KSR* an obviousness rejection under U.S.C. § 103 does not actually require a test of a "reasonable expectation of success". In the instant case, the use of a soluble TNF receptor as a "ligand binding partner" in the invention of Capon is a predictable variation. The skilled artisan would recognize would that the immunoglobulin fusion would predictably improve a soluble TNF receptor (for use in purification of its ligand) in the same manner as Capon teaches generally for other ligand binding partners (e.g., extracellular domains of receptors).

Second, the statement in the Lesslauer Declaration merely suggests a possibility (i.e., that it "could have been possible" the fusion protein would not bind TNFα), and does not provide any evidence that the skilled artisan would have had a greater expectation that it would not bind than an expectation that it would bind. The corollary of the statement in the Declaration is that it "could have been possible" that the fusion protein would have been able to bind TNFα. The Declaration does not provide any indication or evidence as to which of these possibilities would have been held to be more likely to prevail. The Declaration provides no evidence showing why an IgG fusion would predictably create a geometry that would prevent binding. Furthermore, the skilled artisan would have also considered the binding possibilities in view of the teachings of Dembic (1990). Specifically, Dembic also teaches a TNF-binding soluble fragment of the 75kD human TNF receptor that contains sequences that are presumably from the extracellular region (pg 235, left column). This molecule has a different tertiary structure from the full-length receptor yet can bind to TNF. Thus Dembic provides evidence that the C-terminal domain of TNFR2 is not critical to the binding of TNF. Thus, the evidence set forth in the Lesslauer Declaration and the

reference of Dembic has been fully considered, and the preponderance of the evidence supports that the skilled artisan would have predicted that the C-terminal sequences of TNFR2 could be replaced without altering binding.

d. Appellants' argument that the Examiner legally erred in refusing to evaluate the evidence of unexpected results (pg 47).

At page 47, Appellants argue that the Examiner legally erred in refusing to evaluate the evidence of unexpected results. Appellants argue that the "Examiner provided no other comments on the merits of the evidence or any indication that he evaluated the evidence at all" (page 47). Appellants argue that the Examiner must consider all evidence when assessing patentability.

These arguments have been fully considered but are not found to be persuasive. Contrary to Appellants' assertion, the Examiner did provide meaningful consideration of Appellants' evidence. As set forth in MPEP 2145, the Examiner "set forth the facts and reasoning that justify" the conclusion that "the evidence is insufficient to rebut the *prima facie* case of obviousness". This reasoning was as follows.

At page 18 of the 2/23/07 Office Action (Final Rejection), the Examiner stated that "[t]he evidence of unexpected results presented by Appellants is not sufficient to overcome the rejection. Appellants' putative unexpected results appear to be generated using a fusion protein comprising the full-length extracellular domain of the insoluble 75 kD TNF binding receptor and portions of an immunoglobulin molecule. However, as set forth above, in the section "Claim Rejections - 35 U.S.C. 112, 1st paragraph, written description", the specification does not provide a description of this particular species of fusion protein. There is no conception in the specification at the time of filing of this particular species of fusion protein. Therefore, the evidence of unexpected results found with this particular species of receptor-Ig fusion is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon."

Thus, the Examiner did indicate that Appellants' results with the particular species were fully considered, and further acknowledged that they did constitute unexpected results, but did not find this evidence of unexpected results sufficient to

overcome the rejection. Appellants have submitted evidence of unexpected results for species (comprising a full-length extracellular domain of a 75 kD human TNF receptor) encompassed by the claimed genus (a fusion comprising any "soluble fragment" of 75 kD human TNF receptor). However, as set forth in the written description rejection, the specification as originally filed does not provide any teachings pointing to species comprising the full-length extracellular domain of a 75 kD human TNF receptor, and in fact teaches away from such species by repeatedly referring to TNF-binding fragments of the sequence of Figure 4 (SEQ ID NO: 4). The specific use of the entirety of the extracellular domain represents a teaching that goes beyond the original disclosure.

e. Appellants' arguments regarding unexpected results (pg 48-54).

At pages 48-54, Appellants provide a description of the unexpected results found with a species encompassed by the claims, including (i) unexpectedly absent or drastically reduced pro-inflammatory effector functions (pages 49-51); (ii) lack of aggregating ability (pages 51-53); (iii) unexpected thousand-fold increased potency in TNF neutralizing activity (page 53); and (iv) unexpectedly increased binding affinity and kinetic stability (page 54).

(i) At pages 49-51, Appellants describe how a fusion protein consisting of "the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other than CH1" had "drastically reduced, if not completely eliminated, effector function as compared to an anti-TNF antibody". Appellants argue that this result is unexpected in view of the teachings of the art, including Capon (used in the rejection), which teaches that its hybrid immunoglobulin fusion proteins were expected to retain immunoglobulin effector functions.

Appellants' arguments have been fully considered but are not sufficient to overcome the rejection. The Examiner does not dispute that the drastically reduced effector function observed for a fusion protein consisting of "the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other than CH1" was an unexpected result. However, as stated above, there is no conception in the specification at the time of filing of the particular species of fusion protein

containing the full-length extracellular domain of the 75 kD human TNF receptor. Therefore, the evidence of unexpected results found with this particular species is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon.

(ii) At pages 51-53, Appellants describe how a fusion protein consisting of "etanercept" (citing the same reference as in section (i) above) failed to form "high molecular aggregates when combined with TNF" as observed with two different anti-TNF antibodies. Appellants argue that this result is unexpected in view of the presence of an Fc region in the fusion protein which the skilled artisan would have predicted to "form aggregated complexes with trimeric TNF ligand" (page 52).

Appellants' arguments have been fully considered but are not sufficient to overcome the rejection. The Examiner does not dispute that the failure of a fusion protein consisting of "the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other than CH1" to form aggregating complexes was an unexpected result. However, as stated above, there is no conception in the specification at the time of filing of the particular species of fusion protein containing the full-length extracellular domain of the 75 kD human TNF receptor. Therefore, the evidence of unexpected results found with this particular species is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon.

(iii) At page 53, Appellants describe how a fusion protein consisting of a "soluble p75 TNFR fusion protein within the scope of the claims" had "an unexpected 50-fold improvement in TNF neutralizing potency in *in vitro* biological activity assays, compared to the unfused, soluble p75 TNFR". The evidence is provided from the publication of Mohler (1993; page B-181 of the Appeal Brief). Appellants argue that this result is unexpected in view of the teachings of the art such as Capon, which teaches "no such increase in potency" for other "immunoglobulin fragment fusions such as CD4-IgG".

Appellants' arguments have been fully considered but are not sufficient to overcome the rejection. Mohler does not describe the exact sequence of the extracellular domain of the 75 kD human TNF receptor used in immunoglobulin fusion. However, Figure 1 of Mohler (page 1550) shows that the extracellular domain of the

fusion does include all four domains of said TNF receptor. Dembic (1990) teaches that the first domain consists of residues 17-54 of the receptor (see Figure 2 on page 233 of Dembic, 1990). The instant specification does not teach use of a soluble fragment comprising these residues. In particular the protein sequence of Figure 4 (SEQ ID NO: 4) consists only of residues 49-439 of the full-length receptor taught by Dembic, and thus any fragment of this receptor would not include residues 17-49 of the sequence used by Mohler. Furthermore, the post-filing date art (Chan, 2000) provides evidence that a region consists of amino acids 10-54 is required for TNF binding. Thus, while the Examiner does not dispute that the increase in TNF neutralizing potency observed by Mohler was an unexpected result, there is no conception in the instant specification at the time of filing of the particular species of fusion protein containing the full-length extracellular domain of the 75 kD human TNF receptor as used by Mohler. Therefore, the evidence of unexpected results found with this particular species is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon.

(iv) At page 54, Appellants refer to results described in Lesslauer Declaration A (Appendix B-129 of the Appeal Brief). The Declaration describes a fusion protein consisting of "the soluble extracellular domain of the 75 kD TNF receptor" and "the heavy chain of a human IgG3 molecule which is missing the CH1 domain and contains the hinge, CH2 and CH3 domains". The Declaration includes results showing that this fusion protein had "an excellent binding activity". The Declaration also states that the fusion protein had "an unexpectedly higher kinetic stability" and "a surprisingly improved inhibition of the effect of TNF in biological cell culture tests"; the results leading to these conclusions are shown in comparison to results observed for the isolated soluble extracellular domain. Appellants argue that these results are unexpected in view of the teachings of Capon (cited in the rejection) teaching that a CD4/IgG fusion bound to its ligand with the same kinetic stability as the soluble, unfused CD4.

Appellants' arguments have been fully considered but are not sufficient to overcome the rejection. First, the Examiner disputes that the "excellent binding activity" was an unexpected result. The Declaration does not define "excellent binding activity" or distinguish this term from "binding activity" in general. For the reasons set forth above

in section "c", the skilled artisan would have predicted that a fusion of the extracellular domain of the 75 kD TNF receptor with dimeric immunoglobulin sequences would be able to bind to TNF. Furthermore, the Figure on page B-138 does not show any difference in the initial binding activity between the fusion protein and a soluble extracellular domain. Second, it is not disputed that the "kinetic stability" and "improved inhibition of TNF" observed for a fusion protein consisting of "the soluble extracellular domain of the 75 kD TNF receptor" and "heavy chain of a human IgG3 molecule which is missing the CH1 domain and contains the hinge, CH2 and CH3 domains" was an unexpected result. However, as stated above, there is no conception in the specification at the time of filing of the particular species of fusion protein containing the full-length extracellular domain of the 75 kD human TNF receptor. Therefore, the evidence of unexpected results with this particular species is not sufficient to overcome the obviousness of modifying the teachings of Dembic in view of Capon.

2. The obviousness rejection of claims 105 and 113 (pg 55-56).

In this section, Appellants advance the same arguments as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (as in sections 1a-1e above). Appellants further argue that the claims are limit to immunoglobulin IgG_1 isotype and that the evidence shows unexpected results with respect to improved TNF binding and neutralization for both IgG_1 and IgG_3 isotypes and additional unexpected results with respect to reduction of effector function and absence of aggregation ability for IgG_1.

These arguments have been fully considered but are not found to be persuasive. The repeated arguments have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130. With respect to the IgG isotype recited in these claims (IgG_1), Capon specifically teaches use of this isotype, as set forth in the rejection (Capon teaches IgG_1 in column 14, line 66). Therefore, Appellants' unexpected results with respect to this isotype is not found to be persuasive for the same reasons as described above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

3. The obviousness rejection of claims 106, 125, 126 and 128 (pg 56).

In this section, Appellants advance the same arguments as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (as in sections 1a-1e above). Appellants further argue that the claims are limit to immunoglobulin IgG_1 isotype. Appellants argue that the evidence shows unexpected results with respect to improved TNF binding and neutralization for both IgG_1 and IgG_3 isotypes and additional unexpected results with respect to reduction of effector function and absence of aggregation ability for IgG_1.

Appellants further argue that the claims recite more peptide sequences including SEQ ID NOs: 8, 9, 12 and 13 and that this "recitation of further sequence characterizing TNFR provides for different scope and patentability considerations".

These arguments have been fully considered but are not found to be persuasive. The repeated arguments have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130. With respect to the IgG isotype recited in these claims (IgG_1), Capon specifically teaches use of this isotype, as set forth in the rejection (Capon teaches IgG_1 in column 14, line 66). Therefore, Appellants' unexpected results with respect to this isotype is not found to be persuasive for the same reasons as described above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130. With respect to the additional peptide sequences of SEQ ID NO: 8, 9, 12 and 13, the 75 kD human TNF receptor sequence taught by Dembic includes each of these sequences at residues 43-47 (IIB, SEQ ID NO: 8); 66-69 (IIF, SEQ ID NO: 12); 278-284 (IIG, SEQ ID NO: 13); and 324-339 (IIC, SEQ ID NO: 9). SEQ ID NO: 8 and 12 are in the extracellular domain of said receptor, and SEQ ID NO: 13 and 9 are in the intracellular region of said receptor. Therefore, the rejection of claims 106, 125, 126 and 128 was set forth for the same reasons as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 and is maintained for the same reasons as for these claims.

4. The obviousness rejection of claim 114 (pg 56-58).

In this section, Appellants advance the same arguments as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (as in sections 1a-1e above).

Appellants further argue that the rationale for combining Dembic and Capon cannot be applied to this claim. Appellants argue that the assertion that "preparation of sterile pharmaceutical compositions was motivated, without explaining why affinity purification composition needs to contain a pharmaceutically acceptable carrier material" is completely unsupported by any evidence, contrary to controlling precedent" (page 57). Appellants further argue that it is not rational to assert that the affinity purification compositions need to contain a "sterile pharmaceutically acceptable carrier material" (page 57). Appellants further stated on page 40 that "[t]he Examiner did not explain why affinity purification compositions, which are not intended for administration to humans, would require sterile isotonic formulations".

These arguments have been fully considered but are not found to be persuasive. The repeated arguments have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

Claim 114 is directed to "a pharmaceutical composition comprising the recombinant protein of any of claims 62, 107, 134 or 135 and a pharmaceutically acceptable carrier material". There is no requirement in this claim that either the composition or the carrier material is "sterile" or "isotonic", and the Examiner did not assert there was motivation to prepare a "sterile" and/or "isotonic" pharmaceutical composition or to include a "sterile" pharmaceutically acceptable carrier material. The instant specification does not provide a limiting definition of a "pharmaceutical composition" or "pharmaceutically acceptable carrier material" indicating that either must be "sterile". In fact, the specification does not appear to use the word "sterile". Therefore, the claim broadly encompasses both sterile and non-sterile pharmaceutical compositions. A "pharmaceutical composition" is not required to be "sterile" or "isotonic". For example, water can be orally administered without being sterile or isotonic, and thus proteins placed in water are encompassed broadly by the terms "pharmaceutical composition" and "pharmaceutically acceptable carrier". Thus, the rejection does not require an explanation of why pharmaceutical compositions for affinity purification would need to be sterile or isotonic, because pharmaceutical compositions are not required to be sterile or isotonic. Finally, as set forth in the

rejection, the recitation of “a pharmaceutical composition” in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed product from a product taught in the art. Therefore, claim 114 encompasses any composition comprising a recombinant protein of claims 62, 107, 134 or 135 and a pharmaceutically acceptable carrier material. As described in the rejection, the teachings of Capon include recombinant production of hybrid immunoglobulins in cell culture (column 26, lines 24-26), that CHO cells are suitable eukaryotic cells for production of hybrid immunoglobulins (column 29, line 37), purification of the hybrid immunoglobulin from cell cultures following expression in host cells (column 30, line 26-27), and placement of the hybrid immunoglobulin in "sterile, isotonic formulations" that are "preferably liquid" and "ordinarily a physiologic salt solution" (column 31, lines 4-8). Such solutions meet the definition of a “pharmaceutically acceptable carrier material" (as in claim 114). These formulations "optionally are administered" (column 31, line 5), indicating administration is not required. Thus, placement of the hybrid immunoglobulin in these solutions is not limited to use for administration. As described in the rejection, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to further include the hybrid TNF receptor-immunoglobulin in a pharmaceutically acceptable carrier material. The person of ordinary skill in the art would be motivated to do so in order to resuspend the hybrid immunoglobulin for use following purification. The person of ordinary skill in the art would have expected success because Capon teaches the necessary procedures for purification and resuspension of the hybrid immunoglobulin.

5. The obviousness rejection of claim 121 (pg 58).

In this section, Appellants advance the same arguments as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (as in sections 1a-1e above). Appellants further argue the scope of claim 121 differs from claim 62 because although it depends from claim 62 it limits the fusion protein to one that "consists of" of part (a) and part (b). Appellants argue that this excludes embodiments with additional sequences, such as a linker between the two parts, and that the "scope and patentability considerations with

respect to this claim differ", and that "the evidence of unexpected results was generated with a fusion protein that consists of a TNF-binding soluble fragment of p75 TNFR fused to all of the domains of an IgG heavy chain constant region other than CH1" (pg 58).

These arguments have been fully considered but are not found to be persuasive. The repeated arguments have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

With respect to the language reciting "consists of", this argument has been fully considered but is not found to be persuasive. As set forth in the rejection, each of the claims encompasses a protein that "consists of" parts (a) and (b) ("comprising" being broader than "consisting"), and the rejection of each claim was based on such a protein. As noted in the rejection, it would have been obvious to fuse the extracellular domain taught by Dembic to the immunoglobulin sequences taught by Capon. Thus, the resultant fusion protein would "consist" of the two parts, and is the basis for the rejection of the claims. Therefore, the rejection of claim 121 is maintained for the same reasons as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

6. The obviousness rejection of claim 127 (pg 58-59).

In this section, Appellants advance the same arguments as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (as in sections 1a-1e above). Appellants further argue the scope of claim 127 differs from claim 62 because although it depends from claim 106 it limits the fusion protein to one that "consists of" of part (a) and part (b). Appellants argue that this excludes embodiments with additional sequences, such as a linker between the two parts, and that the "scope and patentability considerations with respect to this claim differ", and that "the evidence of unexpected results was generated with a fusion protein that consists of a TNF-binding soluble fragment of p75 TNFR fused to all of the domains of an IgG heavy chain constant region other than CH1" (pg 58).

These arguments have been fully considered but are not found to be persuasive. The repeated arguments have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

With respect to the language reciting "consists of", this argument has been fully considered but is not found to be persuasive. As set forth in the rejection, each of the claims encompasses a protein that "consists of" parts (a) and (b) ("comprising" being broader than "consisting"), and the rejection of each claim was based on such a protein. As noted in the rejection, it would have been obvious to fuse the extracellular domain taught by Dembic to the immunoglobulin sequences taught by Capon. Thus, the resultant fusion protein would "consist" of the two parts, and is the basis for the rejection of the claims. Therefore, the rejection of claim 121 is maintained for the same reasons as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

7. The obviousness rejection of claims 131 and 134-136 (pg 59-60)

In this section, Appellants advance the same arguments as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (as in sections 1a-1e above). Appellants further argue the scope of the claims differ because they limits the fusion protein to one that "consists of" or "consisting of" part (a) and part (b). Appellants argue that this excludes embodiments with additional sequences, such as a linker between the two parts, and that the "scope and patentability considerations with respect to this claim differ", and that "the evidence of unexpected results was generated with a fusion protein that consists of a TNF-binding soluble fragment of p75 TNFR fused to all of the domains of an IgG heavy chain constant region other than CH1" (pg 58). Appellants further argue that the claims are limit to immunoglobulin IgG_1 isotype. Appellants argue that the evidence shows unexpected results with respect to improved TNF binding and neutralization for both IgG_1 and IgG_3 isotypes and additional unexpected results with respect to reduction of effector function and absence of aggregation ability for IgG_1.

These arguments have been fully considered but are not found to be persuasive. The repeated arguments have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

With respect to the language reciting "consists of", this argument has been fully considered but is not found to be persuasive. As set forth in the rejection, each of the claims encompasses a protein that "consists of" parts (a) and (b) ("comprising" being

broader than "consisting"), and the rejection of each claim was based on such a protein. As noted in the rejection, it would have been obvious to fuse the extracellular domain taught by Dembic to the immunoglobulin sequences taught by Capon. Thus, the resultant fusion protein would "consist" of the two parts, and is the basis for the rejection of the claims. Therefore, the rejection of claim 121 is maintained for the same reasons as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

With respect to the IgG isotype recited in these claims (IgG_1), Capon specifically teaches use of this isotype, as set forth in the rejection (Capon teaches IgG_1 in column 14, line 66). Therefore, Appellants' unexpected results with respect to this isotype is not found to be persuasive for the same reasons as described above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

8. The obviousness rejection of claim 137 (pg 60-62).

In this section, Appellants advance the same arguments as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (as in sections 1a-1e above).

Appellants further argue that claim 137 is limited to immunoglobulin IgG_1 isotype. Appellants argue that the evidence shows unexpected results with respect to improved TNF binding and neutralization for both IgG_1 and IgG_3 isotypes and additional unexpected results with respect to reduction of effector function and absence of aggregation ability for IgG_1.

Appellants further argue that the rationale for combining Dembic and Capon cannot be applied to this claim. Appellants argue that the assertion that "preparation of sterile pharmaceutical compositions was motivated, without explaining why affinity purification composition needs to contain a pharmaceutically acceptable carrier material" is completely unsupported by any evidence, contrary to controlling precedent" (page 57). Appellants further argue that it is not rational to assert that the affinity purification compositions need to contain a "sterile pharmaceutically acceptable carrier material" (page 57). Appellants further stated on page 40 that "[t]he Examiner did not explain why affinity purification compositions, which are not intended for administration to humans, would require sterile isotonic formulations".

These arguments have been fully considered but are not found to be persuasive. The repeated arguments have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

With respect to the IgG isotype recited in these claims (IgG_1), Capon specifically teaches use of this isotype, as set forth in the rejection (Capon teaches IgG_1 in column 14, line 66). Therefore, Appellants' unexpected results with respect to this isotype is not found to be persuasive for the same reasons as described above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130.

Claim 137 is directed to "a pharmaceutical composition comprising the recombinant protein of any of claim 105 and a pharmaceutically acceptable carrier material". The arguments with respect to the motivation to create a "pharmaceutical composition" and "pharmaceutically acceptable carrier material" have been fully considered but are not found to be persuasive and are maintained for the same reasons as for claim 114 above.

C. The rejection of claims 140-144 under 35 U.S.C. 112, first paragraph (pg 62-66).

In this section of the Appeal Brief filed on 2/28/08, Appellants provide a "Brief Statement of the Relevant Prosecution History" (pages 62-63) and then address each rejection. No dispute is made regarding Appellants' description of the prosecution history. Appellants' arguments are addressed in the order presented in the Appeal Brief.

1. The new matter rejection of claims 140-144 under 35 U.S.C. 112, first paragraph (pg 63-65).

Appellants argue that this rejection should be reversed because Appellants' deposit was in full compliance with applicable case law. Appellants argue that the Examiner rejected the claims on that grounds (1) that the N227 plasmid was not named in the specification and (2) N227 cannot be a DNA described in the specification because it contains more sequence (e.g., signal sequence), than is displayed in the partial DNA sequence of Figure 4, which does not contain any signal sequence.

With respect to the first grounds as characterized by Appellants, Appellants point to the 2001 written description guidelines and *Enzo, supra* and argue that case law and USPTO rules require that the description is sufficient to permit verification that the deposited biological material is in fact that disclosed, but not that the specification include the specific name or designation of the deposited biological preparation. Appellants argue that the instant specification describes cDNA encoding insoluble and soluble fragments of "TNF binding proteins having an apparent molecular weight of 65 kD/75 kD" and that the Third Declaration Lesslauer Declaration under 35 USC 1.132 (Appendix B-141) provides sufficient verification that the deposited N227 plasmid includes DNA encoding insoluble as well as soluble fragments of this 65kD/75kD TNF receptor. Appellants further argue that "description of a DNA encoding an identified protein should be sufficient to support a deposit of such a DNA" and in support point to the Federal Circuit's non-precedential decision in *Evans Medical Ltd v. American Cyanamid Co.* (1999).

These arguments have been fully considered but are not found to be persuasive. The Examiner disputes Appellants' characterization of the grounds for the rejection. The rejection of claims 140-144 under for including new matter was based on the grounds that (1) there is no cDNA taught in the specification encoding the full-length 75 kD TNF receptor and (2) there is no clear description in the specification as originally filed of the specific DNA construct designated N227 (stated in the Lesslauer Declaration of 11/16/07 as being found in the deposit PTA 4792 recited in claim 140). In the arguments, Appellants appear to interpret grounds (2) as being because "the N227 plasmid was not named in the specification". However, the new matter rejection was not based on the grounds that the specification does not contain the specific name or designation of the deposited biological preparation, but rather because there is no description in the specification as originally filed for the specific DNA construct designated N227; nor does the concept of the specific construct flow naturally from the disclosure of the specification. Appellants amended the specification at page 10, line 34, to include reference to the deposit after the word "insoluble" in a sentence that originally read, "DNA sequences that code for insoluble as well as soluble fractions of TNF-

binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred". However, the original teaching was directed to a genus of DNA sequences, because the encoded "insoluble …fractions", while limited to those that bind TNF and have a particular weight, are not limited to any particular sequence and thus encompass any variant with one or more amino acid changes that retains TNF-binding and the recited weight. The specification specifically envisions DNA variants with one or more deletions, substitutions and additions that retain TNF-binding (e.g., page 10, line 1-9). The specification does not teach any particular sequence within this genus (i.e., each variant encompassed by this genus is a separate species that is not particularly taught). Thus, the specification does not describe a specific species such as that of the deposited sequence. By analogy, the claims would also include new matter if Appellants amended the same sentence in the specification to include a reference to a specific Sequence Identifier not specifically taught in the original specification (e.g., "DNA sequences that code for insoluble (SEQ ID NO: X) as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred"). With respect to *Evans Medical Ltd v. American Cyanamid Co.* (1999), this decision is non-precedential and unpublished, and therefore is not binding as precedent in regard to the fact pattern in the instant application. Furthermore, the argument allegedly supported by *Evans* (i.e., that a "description of a DNA encoding an identified protein should be sufficient to support a deposit of such a DNA") is not found to be persuasive because an original description of a genus of DNA (encoding a genus of proteins) is not sufficient to support a deposit of a particular species of such DNA. As stated in MPEP 2163, "The proscription against the introduction of new matter in a patent application (35 U.S.C. 132 and 251) serves to prevent an applicant from adding information that goes beyond the subject matter originally filed". Here, the specific sequence deposited by Appellants is added information that goes beyond the broader teaching of a genus of DNA sequences that code for insoluble fractions of TNF-binding proteins having apparent molecular weight of 65 kD/75 kD. In *Evans*, the deposit of concern (an antibody) did not go beyond the teachings of the original specification.

With respect to the second grounds as characterized by Appellants, Appellants argue that they clearly contemplated a full length 75 kD TNFR for the reasons noted in section VII.A.I of the Appeal Brief, and therefore it is not proper to reject the claims on the basis that the deposited cDNA contains more sequence than Figure 4 of the application. Appellants further argue that the claims recite the soluble fragment encoded by the DNA construct and therefore exclude the presence of a signal sequence, because it is understood in the art the extracellular domain excludes the signal sequence. Appellants argue that it is common for DNA deposits to include more than the portion of sequence claimed and point to *Enzo* (2002) in support.

These arguments have been fully considered but are not found to be persuasive. As above, the Examiner disputes Appellants' characterization of the grounds for the rejection. To reiterate, the rejection of claims 140-144 under 112, 1st paragraph for including new matter was based on the grounds that (1) there is no cDNA taught in the specification encoding the full-length 75 kD TNFR receptor (2) there is no clear description in the specification as originally filed of the specific DNA construct designated N227 (stated in the Lesslauer Declaration of 11/16/07 as being found in the deposit PTA 4792 recited in claim 140). In their arguments in response to rejection, Appellants appear to interpret grounds (1) as being based on the grounds that "N227 cannot be a DNA described in the specification because it contains more sequence (e.g., signal sequence), than is displayed in the partial DNA sequence of Figure 4, which does not contain any signal sequence. However, the new matter rejection was not based on the grounds that N227 contains more sequence that displayed in Figure 4, but rather because claim 140 requires a "cDNA insert" and there is no cDNA described in the specification that encodes the full-length 75 kD TNFR-2. Claims 140-144 recite a protein comprising a TNF-binding soluble fragment of an amino acid sequence encoded by a "cDNA insert" of a plasmid deposited with the ATCC under accession number PTA 7942. The term "cDNA" is short for "complementary DNA" and refers to a specific type of DNA that is synthesized from a complementary RNA strand. Thus, the insert found in the deposit must be cDNA and encode an amino acid sequence with a soluble fragment that can bind TNF. The Lesslauer Declaration of 11/14/06 clearly identifies the

deposited material as related to the p75 TNFR. However, the only cDNA insert in the specification related to the 65 kD/75 kD TNF-binding protein is the partial cDNA sequence (SEQ ID NO: 3) shown in Figure 4 that encodes a protein sequence (SEQ ID NO: 4) that is missing a portion of the extracellular domain required for TNF binding. Thus, there is no support in the specification at the time of filing for a cDNA insert encoding a TNF-binding soluble p75 TNFR, for example the full-length 75 kD TNFR. Furthermore, the arguments presented in section VII.A.1 do not include any arguments for possession of a cDNA sequence encoding full-length 75 kD TNFR. Furthermore, while a deposit may include more sequence than that taught the specification (such as a vector sequence), the claimed portion must be fully described in the specification. The claim refers to the cDNA insert and the Lesslauer Declaration refers to the a construct containing "DNA sequence which includes sequence encoding the signal sequence and the extracellular domain of human p75 tumor necrosis factor receptor (TNFR)"; however, no cDNA containing signal sequence or the full-length extracellular domain is described in the specification.

2. The enablement rejection of claims 140-144 under 35 U.S.C. 112, first paragraph (pg 65-66).

As set forth in the section of this Examiner's Answer titled "Grounds of Rejection", subsection "Withdrawn Claim Rejections – 35 USC 112, first paragraph, enablement", this rejection has been *withdrawn* for the reasons set forth therein.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Zachary C Howard/

Examiner, Art Unit 1646

Conferees:

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646

/Robert A. Wax/
Quality Assurance Specialist
Technology Center 1600